Cardiac safety of methylphenidate among pediatric patients with ADHD: a nationwide self-controlled case series study

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Cardiac safety of methylphenidate among pediatric patients with ADHD: a nationwide self-controlled case series study

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Objective To evaluate the association between the use of methylphenidate and cardiac outcomes in children.

Design Self-controlled case-series analysis.

Setting Nationwide health insurance database between January 1, 2007 and December 31, 2011, South Korea.

Participants 889 pediatric patients (aged 17 years or younger) who had experienced an incident cardiac event (arrhythmias, hypertensive disease, myocardial infarction, stroke, and heart failure) and at least one incident prescription for methylphenidate between January 1, 2008 and December 31, 2011.

Main outcome measures Cardiac outcomes were defined as having all arrhythmias (ICD-10: I44, I45, I47, I48, I49), hypertension (ICD-10: I10-I15), myocardial infarction (MI) (ICD-10: I21), ischemic stroke (ICD-10: I63), and heart failure (ICD-10: I50) as either a primary or secondary diagnosis. Incidence Rate Ratios (IRRs) were calculated adjusted for time-varying comorbidity and co-medication. IRRs and their 95% confidence intervals (CIs) were calculated using conditional Poisson regression.

Results A significant increased risk was observed for any cardiac outcome for all exposed time (IRR=1.4, 95% CI: 1.29-1.52). Increased risk of arrhythmias (IRR=1.56, 95% CI: 1.41-1.72) was observed in all exposed risk periods. Stroke risk was elevated only in the risk periods between 8 and 56 days, while heart failure risk was elevated only in risk period of 56 days and beyond. No increased MI risk was identified at any time during exposure.

Conclusion A significantly increased risk of cardiac outcomes was found with methylphenidate use. The risk benefit balance of methylphenidate should be carefully considered, particularly in children with mild disease.

Keywords: methylphenidate, attention-deficit hyperactivity disorder (ADHD), self-controlled case series study, database, cardiac disease

Introduction

Millions of children are currently being treated for attention-deficit hyperactivity disorder (ADHD) worldwide.[1] ADHD medicines have been shown to be efficacious in reducing symptoms of impulsivity and hyperactivity but these must be weighed up against a range of adverse side effects.[2] Concerns have been expressed about possible cardiac effects of the common treatments, namely methylphenidate.[3] Large retrospective, population-based cohort studies have been performed, however, these studies did not find evidence that methylphenidate was associated with an increase in risk of myocardial infarction (MI), or stroke.[4-7] A systematic review reported that findings of observational studies of children and adolescents were variable and suggested that statistical power was limited as the absolute risk of cardiac events is low in this population and the study designs utilized meant that confounding could not be ruled out.[8] Case reports continue to be made and five case reports of life-threatening heart failure have been reported from Sweden,[9] and small but statistically significant increases in blood pressure have been reported in children and adolescents.[10] Despite these latter reports, no observational study has been performed for heart failure or hypertensive disease associated with methylphenidate.

The aim of this study was to explore the cardiac safety of methylphenidate for a number of cardiac outcomes including arrhythmia, hypertension, stroke, MI, and heart failure using the self-controlled case series method. Using this technique, which is a within person design, we compared the incidence of each cardiac outcome among children during periods in which they were exposed with periods in which they were not exposed to methylphenidate, thus eliminating confounding between individuals.

Methods

Database

The Korea National Health Insurance Service (NHIS) claims database was used for this study. The National Health Insurance (NHI) program was initiated in Korea in 1977 and achieved universal coverage of the entire Korean population by 1989. Accordingly, the database contains all information on the diagnoses and prescribed medications for approximately 50 million Koreans.[11]. The claims data for pediatric patients (aged 17 years or younger) who were diagnosed with ADHD (ICD-10, F90) that had been submitted by healthcare providers from January 1, 2007 through December, 31, 2011 were obtained. The NHIS database included an anonymized code representing each individual together with age, gender, diagnoses, and prescription drugs. Information on prescribed drugs included generic name, prescription date, duration, and route of administration. All diagnoses had been coded according to the International Classification of Disease, Tenth Revision (ICD-10). All researchers who wish to use the NHIS database and its data subsets are required to sign a written agreement declaring that they have no intention of attempting to obtain information that could potentially violate the privacy of patients or healthcare providers. The study protocol was approved by the Institutional Review Board of the Korea Institute of Drug Safety and Risk Management. Obtaining informed consent from the study population was waived by the board. A previous validation study compared the diagnoses derived from the HIRA database with the actual diagnoses in the patient medical records. The overall positive predictive value of the diagnoses was 83.4%.[12]

Self-controlled case series design

The self-controlled case-series design is derived from the cohort design. It minimizes confounding because the patient acts as their own control. The within-person design controls for fixed known and unknown confounders, such as genetic factors. It relies on within-person comparisons in a population of individuals who have both the outcome and exposure of interest.[13,14] This design can be particularly useful when using secondary healthcare data for pharmacoepidemiological research and might be useful in screening for adverse drug effects.[15]

Patient involvement and study subject.

There was no patient involvement in this study. The study subjects were composed of pediatric (aged 17 years or younger) ADHD (ICD-10, F90) patients who initiated methylphenidate and had an incident cardiac outcome between 1 January 2008 and 31 December 2011. Cardiac outcomes were defined as arrhythmias (ICD-10: I44, I45, I47, I48, I49), hypertension (ICD-10: I10-I15), myocardial infarction (MI) (ICD-10: I21), ischemic stroke (ICD-10: I63), and heart failure (ICD-10: I50) as either a primary or secondary diagnosis. We only included the first cardiac event to avoid potential bias of the second event being influenced by the first event.[13]

Patients were considered new users of methylphenidate if they had not received a prescription during the preceding one year. The index date was defined as the first prescription date of methylphenidate. We excluded the following patients: (a) those with pre-existing cardiac events during the preceding one year; and (b) children with a cardiac outcome recorded on the same day as the first methylphenidate prescription. The inclusion of only new users with incident outcome, ensured no bias due to the influence of previous

medication use and outcome. (Figure 1) The observation period started at the date of 1, January, 2008 and ended at 31, December, 2011. We found 5 cases of death after the diagnosis of cardiac outcome, and for these cases follow up time was censored at date of death.

Exposure Assessment

We calculated the length of exposure using information on prescription date, and prescribed days in the database. We compared the incidence rate between the unexposed and exposed period and between unexposed and exposed time partitioned into the following risk periods: 1-3 days, 4-7 days, 8-14 days, 15-28 days, 29-56 days, and >56 days. The risk periods were defined based on the quantile values for the distribution of prescribed days. The figure shows how we classified the follow-up time for an individual with respect to exposure. (Figure 2)

To verify the robustness of our results, we performed several sensitivity analyses. First applying a wash-out period and second a pre-exposure risk period was included. A wash-out period was defined considering the possibility that the patients might not take their medicine strictly according to their prescription. Washout periods were defined as 1-3 days, 4-7 days, and 8-14 days after the end date of prescription. Additionally, two consecutive 30-day pre-exposure risk periods were also included prior to the very first prescribed date of medication in the sensitivity analysis. These time periods were based on rehabilitation times for recovery from cardiac events, which is a time period in which ADHD medication is unlikely to be used.

Time-varying confounders

Time-varying covariates were adjusted in the model including age, comorbidities and co-medications. Co-morbidities included depressive episode (ICD-10: F32-F33, F34.1, F41.2), tic disorders (ICD-10: F95), emotional disorders with onset specific to childhood (ICD-10: F93), conduct disorders (ICD-10: F91), manic episodes (ICD-10: F30), bipolar affective disorders (ICD-10: F31) and mental retardation (ICD-10: F70-79). Co-medications included atomoxetine, antipsychotics (ATC: N05A), antidepressants (ATC: N06A), anxiolotics (ATC: N05B), antiepileptics (ATC: N03A), and anticholinergic agents (ATC: N04A).

Statistical Analysis

Incident rate ratios (IRRs) in periods of time exposed to methylphenidate compared with unexposed periods were calculated. We estimated the adjusted rate ratios and their 95% confidence intervals (CIs) using conditional Poisson regression in each pre-determined risk period. We evaluated the differential effects of methylphenidate for the composite cardiac outcome, and each cardiac outcome: arrhythmias, hypertension, MI, stroke, and heart failure. We also performed sensitivity analysis according to the definition of wash out period and risk period prior to methylphenidate use to confirm the robustness of main results. We used the SAS statistical application program (release 9.4) for all statistical analyses. We considered a two tailed value of $P<0.05$ to be statistically significant.

Results

A total of 889 eligible participants were identified and included in the final analysis. This included 557 cases of arrhythmias, 248 hypertensive disease, 34 MI, 34 stroke, and 24 heart failure. Median age was 15 years old at first exposure, and 13 years old at first outcome. Mean duration of methylphenidate exposure was 0.5 years, and the boys constituted 78% of the cohort. Depressive episode was most common comorbidity among study subjects (30.9%), and antidepressants (36.2%), and antipsychotics (26.0%) were co-prescribed frequently. (Table 1)

Increased risk was observed with methylphenidate exposure for any cardiac outcome (IRR=1.4, 95% CI: 1.29-1.52). Higher risk was observed 1-3 days after initiation (IRR=2.08, 95% CI: 1.82-.2.39), 4-7 days (IRR=1.72, 95% CI: 1.51-1.97), and 8-14 days (IRR=1.48, 95% CI: 1.32-1.67). According to each specific outcome, the increased risk was observed for arrhythmias (IRR=1.56, 95% CI: 1.41-1.72) in all risk periods. The highest risk was observed in the 1-3 days after initiation (IRR=2.08, 95% CI: 1.82-.2.39), and reduced but remained significantly elevated in 4-7 days (IRR=1.72, 95% CI: 1.51-1.97), and 8-14 days (IRR=1.48, 95% CI: 1.32-1.67). While no increased overall risk was identified for hypertension, when exposure time was partitioned into several risk periods after initiation, a higher risk was observed in the 1-3 and 4-7 days risk periods for this outcome (IRR=1.45, 95% CI 1.1-1.91 and IRR=1.63, 95% CI: 1.3-2.06, respectively). The overall risk of stroke was not significantly raised, however risk was elevated in the early risk periods (8-14 days, 15-28 days and 29-56 days) but was not significantly raised with longer term treatment. Conversely the risk of heart failure was only significantly elevated with longer-term treatment of greater than 56 days (IRR=4.39, 95% CI: 2.4-8.02). (Table 2) Sensitivity analysis showed slightly higher risk estimates and confirmed the robustness of our main results. (Table 3)

Discussion

This study found that the risk of cardiac outcomes was increased by 40% with exposure to methylphenidate compared to periods of non-use in the same patients. Overall increased risk for arrhythmias was observed over all time periods assessed. Risk of stroke was found to be elevated after the first week of therapy was complete and remained elevated for 2 months, while risk of heart failure only emerged after two months of continuous therapy. Collectively, these results are consistent with the biological plausibility that the mechanism of action relates to methylphenidates effect on heart rate and blood pressure.[16,17] Delayed effects would be expected to be observed with heart failure and to a lesser extent stroke, while more immediate effects would be expected with arrhythmias, as was observed.

A systematic review of previous observational research investigating the risk of cardiac events with methylphenidate reported that six out of seven studies in children and adolescents did not show an association, however the study designs meant that confounding could not be ruled out.[8] Due to the low number of events, most previous studies in children and adolescent did not have sufficient statistical power. Previous research found no evidence of increased risk for stroke, or MI which was consistent with our overall risk. However, our time based risk analysis suggests that the risk of stroke was elevated in the early risk periods (8-14 days, 15-28 days and 29-56 days). Conversely the risk of heart failure was only significantly elevated with longer-term treatment of greater than 56 days, and 4.39 fold increased risk was observed. No previous observational studies have been performed to investigate the risk of heart failure. This result is of concern and warrants further research. Our results for hypertension varied across the risk periods, however, risk was elevated for the majority of risk periods between 1 and 56 days. It is possible that a form of detection bias has influenced this result because hypertension is non-symptomatic it may have only been detected through routine tests at a scheduled follow-up appointment with their healthcare

provider.. All the other events assessed were symptomatic events, the symptoms of which would precipitate attendance independent of a planned visit.

To the best of our knowledge, this is the first population based self-controlled case series study focusing on the risk of a comprehensive list of cardiac outcomes and the first to assess the temporal association between methylphenidate initiation and cardiac outcomes. Previous research has shown that the self-controlled case series method produces similar risk estimates to a new-users cohort study design and has the advantage of controlling for constant patient-specific confounders due to its with-in person study design.[18] We performed several sensitivity analyses to verify the robustness of our results by applying a wash-out period and a pre-exposure risk. One of the assumptions of the self-controlled case series design is that the occurrence of an event must not alter the probability of subsequent exposures.[13,14] It is possible that experiencing a cardiac outcome may be a contraindication to prescribing methylphenidate. This would lead to a low rate of events in the period leading up to the first period of use, in unexposed time, and may artificially exaggerate the relative rate of events occurring in exposed periods. Several previous studies applying self-controlled case series designs have defined the pre-exposure period to control for potential bias.[19-21] However, our analysis found that incidence in the pre-exposure period was slightly higher compared with the post-exposure period (appendix 1), therefore, this would have produced biased results toward the null, and our sensitivity analysis confirmed the main result was not changed. Higher incidence in the pre-exposure period is consistent with the previous findings that ADHD is more prevalent in the children and adolescents with heart disease than in the general pediatric population.[22] In addition, safety warnings of methylphenidate in Korea, which were disseminated on December, 2009, were not assumed to have influenced the

medical practice in our study (2007-2011), which includes the time periods prior to the safety warnings.

Another assumption of this design is that recurrent outcome events must be independent, that is, the occurrence of one event must not alter the probability of a subsequent event occurring.[13,14] In our study, once a person has had a cardiac event, their short-term risk of experiencing another may be increased. Therefore, events may cluster within independent episodes. We found 10% of children and adolescents had a recurrent diagnosis of cardiac outcomes within 30 days. However, as we previously indicated there was a higher incidence in the pre-exposure period, the events were more clustered in the pre-exposure period compared with post-exposure period, therefore, this would also have produced biased results toward the null. The final assumption is that the occurrence of the event of interest must not censor or affect the observation period.[13,14,18] Our study population covered children and adolescents, and there were only 5 cases of death after the diagnosis of cardiac outcome in 889 study subjects. Farrington et al,[23] and our previous studies using self-controlled case series design[18,20] have shown that this method may be robust to failure of this assumption, and we also found that the main results were not changed when analysis was limited to children who survived until the end of the study.

While the self-controlled case series design adjusts implicitly for constant patient specific confounders it is possible that the association observed may be bias due to time-varying confounders. Antidepressants or antipsychotics are frequently co-prescribed with methylphenidate and may explain some of the association found with cardiac events[24,25]. To account for this possibility, we adjusted all our analyses for time-varying comorbidities and co-medications.

Strengths and Limitations

This study had several strengths. Our study included the entire Korean population rather than a sample and used the claims database for all ADHD patients collected by the NHI program, which covered nearly all inhabitants of Korea. Until recently, evidence of cardiac effects of ADHD medicines was limited to a number of observational studies which had insufficient power to examine rare cardiac events Our results representing a large population in a real-setting suggest that cardiac events are associated with methylphenidate exposure. Second, we performed the self-controlled case series study, which controls for within person unmeasured confounders and has previously been shown to produce similar risk estimates to a new-user cohort study design.[18] In addition, further adjustments were made for other diagnoses and medication use using time-varying confounding adjustment.

Our findings should be interpreted with caution. There is the potential for inaccuracy of coding and incompleteness of records. The outcome measures were limited to patients diagnosed with cardiac outcomes and we may have missed cardiac outcomes not diagnosed. A validation study comparing the diagnosis derived from the health insurance database with the actual diagnosis in patients' medical records in Korea found that the overall positive predictive value of the diagnoses was 83.4%.[12] Additionally, we defined the study outcome as their primary or secondary diagnosis to increase the validity of study outcome by including all possible cases of cardiac events.

Conclusions

This study suggests that methylphenidate exposure was associated with a range of cardiac outcomes. With the increased utilization of ADHD medicines globally, the risk of methylphenidate should be carefully weighed against the benefits of these medicines in children and adolescents.

Contributors: All authors contributed to study design and interpretation of data. JS and BP acquired the database. JS and NLP had the main responsibility for statistical analysis but all authors contributed. JYS, EER, and NLP wrote the manuscript, and all authors reviewed and commented on drafts and approved the final manuscript and the decision to submit for publication. JS is the guarantors of the study, accept full responsibility for the research, had access to the data and controlled the decision to publish.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This study was approved by the institutional review board of the Korea Institute of Drug Safety and Risk Management, Seoul.

Data sharing: No additional data available.

Transparency declaration: The guarantors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Figure1. Self-controlled case series study (Colour Image Attached)

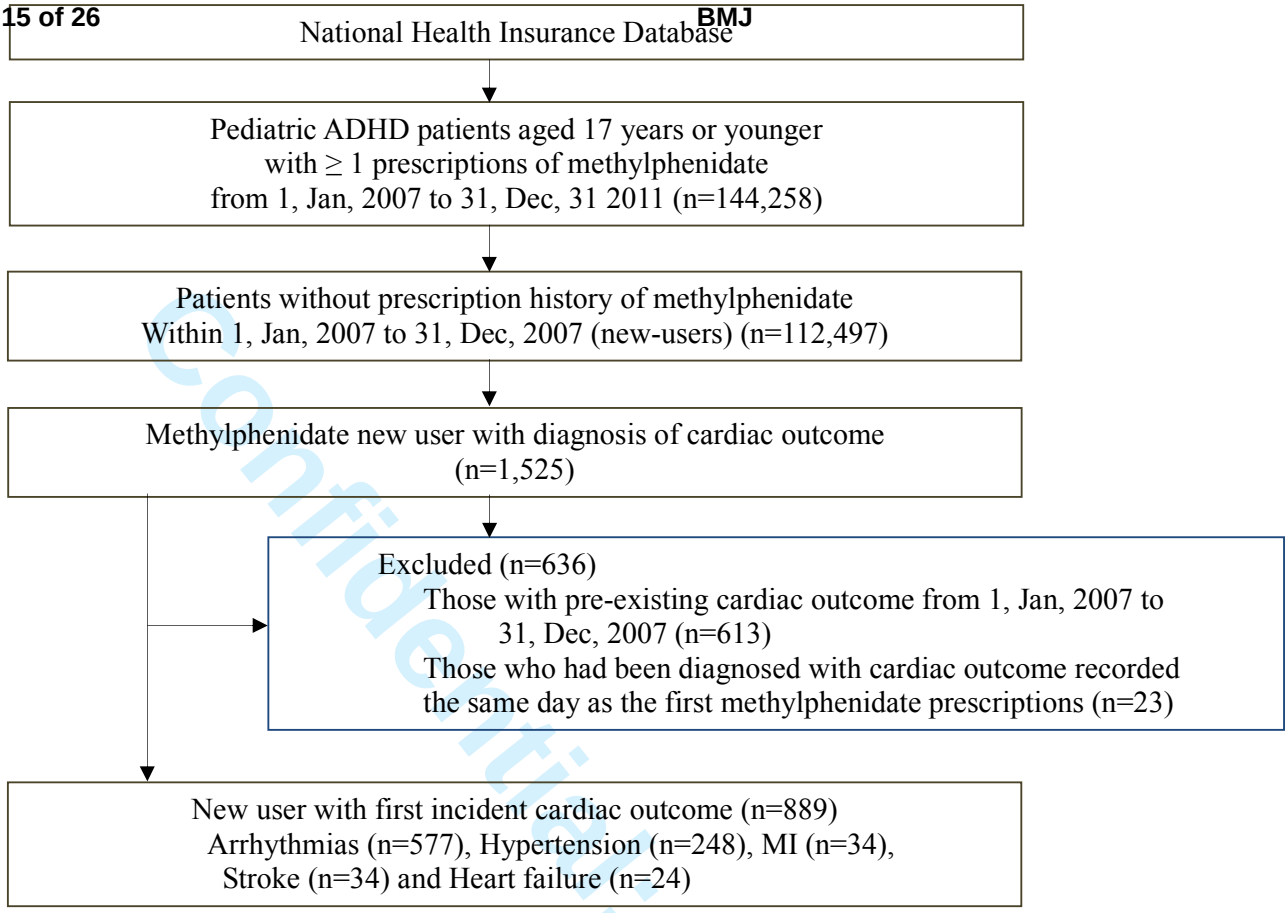

Figure2. Selection of study subjects from the National Health Insurance database in a self-controlled case series design

Table 1. Characteristics of study subject

	Cardiac Outcome	Arrhythmias	Hypertensive disease	Myocardial Infarction	Ischemic Stroke	Heart Failure
Number of patients	889	577	248	34	34	24
Duration of exposure (years)	0.5 (0.1,3)	0.6 (0.1,1.4)	0.4 (0.1,1.2)	0.3 (0.1,0.8)	0.5 (0.1,1.1)	0.2 (0.1, 0.9)
Age at first exposure (median) (q1, q3)	15 (11,17)	15 (11,17)	15 (13,17)	13 (10,17)	11 (11,15)	15 (13,17)
Age at first outcome (median) (q1, q3)	13 (10,15)	13 (9 ,15)	13 (10,16)	11 (8 ,15)	10 (8 ,13)	13 (10,16)
Gender (%), Boys	78	77	81	79	76	75
Comorbidity (%)*						
Depressive episode(F32-F33, F34.1, F41.2)	30.9	29.5	34.7	23.5	20.6	45.8
Tic disorders(F95)	10.6	10.6	11.7	8.8	17.6	8.3
Emotional disorders with onset specific to childhood(E93)	12.1	12.0	10.5	14.7	14.7	16.7
Conduct disorders(F91)	10.3	10.6	11.7	11.8	0.0	8.3
Manic episode(F30)	0.2	0.3	0.0	0.0	0.0	0.0
Bipolar affective disorder(F31)	6.7	7.8	5.2	8.8	2.9	4.2
Mental retardation(F70-F79)	10.7	10.2	10.1	23.5	11.8	8.3
Co-medication (%)**						
Atomoxetine	1.7	1.7	1.2	2.9	2.9	0.0
Antipsychotics (ATC: N05A)	26.0	21.8	25.8	17.6	17.6	20.8
Antidepressants (ATC: N06A)	36.2	35.7	37.5	38.2	17.6	50.0
Antiepileptics (ATC: N03A)	12.9	11.6	11.7	41.2	5.9	29.2
Anticholinergic agents (ATC: N04A)	8.0	8.0	10.1	2.9	8.8	4.2
Anxiolotics (ATC: N05B)	13.0	13.7	14.1	14.7	0.0	20.8

*Comorbidity was defined at least one diagnosis or prescription between January, 1, 2008 AND December, 31, 2011. ** Co-medication was defined as the co-prescription with methylphenidate during the same period.

Table 2. Risk of cardiac outcome before and after methylphenidate

Risk Periods	No. of Outcome	Person-years	Adjusted rate ratio* (95% CI)	
Composite Cardiac Outcome				
Unexposed	659	2,812	1	
Exposed	230	744	**1.4**	(1.29- 1.52)
Times since initiation of methylphenidate				
1-3 days	25	51	**2.08**	(1.82- 2.39)
4-7 days	27	67	**1.72**	(1.51- 1.97)
8-14 days	36	107	**1.48**	(1.32- 1.67)
15-28 days	42	147	**1.28**	(1.14- 1.43)
29-56 days	40	146	**1.24**	(1.1- 1.39)
> 56 days	60	225	**1.3**	(1.17- 1.45)
Arrhythmias				
Unexposed	414	1,797	**1**	
Exposed	163	511	**1.56**	(1.41- 1.72)
Times since initiation of methylphenidate				
1-3 days	20	36	**2.56**	(2.19- 3)
4-7 days	19	47	**1.87**	(1.59- 2.19)
8-14 days	28	74	**1.79**	(1.56- 2.05)
15-28 days	26	102	**1.23**	(1.07- 1.41)
29-56 days	29	98	**1.45**	(1.27- 1.67)
> 56 days	41	155	**1.4**	(1.23- 1.6)
Hypertensive disease				
Unexposed	191	797	**1**	
Exposed	57	195	**0.99**	(0.85- 1.17)
Times since initiation of methylphenidate				
1-3 days	6	13	**1.45**	(1.1- 1.91)
4-7 days	9	18	**1.63**	(1.3- 2.06)
8-14 days	5	28	**0.57**	(0.42- 0.77)
15-28 days	14	40	**1.2**	(0.98- 1.46)
29-56 days	8	41	**0.65**	(0.51- 0.83)
> 56 days	15	55	**0.99**	(0.8- 1.23)
Myocardial Infarction				
Unexposed	29	111	**1**	
Exposed	5	25	**0.75**	(0.45- 1.26)
Times since initiation of methylphenidate				
1-3 days	0	1	**-**	-
4-7 days	0	2	**-**	-
8-14 days	1	3	**1.45**	(0.72- 2.94)
15-28 days	0	5	**-**	-
29-56 days	2	6	**1.27**	(0.73- 2.21)
> 56 days	2	8	**0.98**	(0.53- 1.82)
Ischemic Stroke				
Unexposed	27	109	**1**	
Exposed	7	27	**1.21**	(0.78- 1.86)
Times since initiation of methylphenidate				
1-3 days	0	2	**-**	-
4-7 days	0	2	**-**	-

8-14 days	2	4	**1.99**	(1.17-	3.38)
15-28 days	2	5	**1.67**	(1-	2.78)
29-56 days	2	5	**1.88**	(1.12-	3.17)
> 56 days	1	9	**0.65**	(0.32-	1.32)
Heart Failure					
Unexposed	20	80	**1**		
Exposed	4	16	**1.03**	(0.59-	1.78)
Times since initiation of methylphenidate					
1-3 days	0	1	**-**	-	
4-7 days	0	1	**-**	-	
8-14 days	0	2	**-**	-	
15-28 days	1	3	**1.59**	(0.75-	3.35)
29-56 days	0	3	**-**	-	
> 56 days	3	7	**4.39**	(2.4-	8.02)

* Rate ratio was adjusted for age, comorbidity and co-medication in time-varying method.

Table 3. Sensitivity analysis according to the definition of risk-period

	Cardiac Outcome			Arrhythmias			Hypertension			Myocardial Infarction			Ischemic stroke			Heart Failure		
Risk Periods	Adjusted Rate Ratio (95% % CI)*																	
Primary analysis, absence of pre-exposure period and washout period																		
Exposed vs. Unexposed	1.4	(1.29	-1.52)	1.56	(1.41	-1.72)	0.99	(0.85	-1.17)	0.75	(0.45	-1.26)	1.21	(0.78	-1.86)	1.03	(0.59	-1.78
Secondary analysis, pre-exposure period with washout period																		
Exposed vs. Unexposed	1.73	(1.61	-1.86)	2.02	(1.85	-2.21)	1.07	(0.93	-1.24)	1.01	(0.63	-1.61)	1.43	(0.98	-2.08)	1.33	(0.8	-2.2
Prior to Methylphenidate use																		
31-60 before Rx.	3.18	(2.9	-3.48)	3.24	(2.88	-3.63)	2.27	(1.89	-2.72)	7.31	(5.38	-9.93)	1.9	(1.08	-3.35)	2.86	(1.54	-5.3)
1-30 days before Rx.	1.79	(1.58	-2.02)	1.92	(1.65	-2.24)	1.22	(0.93	-1.58)	4.21	(2.72	-6.53)	1.85	(1.05	-3.26)	5.51	(3.47	-8.74
Times since initiation of methylphenidate																		
1-3 days	2.58	(2.27	-2.93)	3.35	(2.9	-3.87)	1.56	(1.21	-2.01)	-	-	-		-		-	-	
4-7 days	2.13	(1.88	-2.41)	2.45	(2.11	-2.84)	1.76	(1.42	-2.18)	-	-	-		-		-	-	
8-14 days	1.84	(1.65	-2.05)	2.36	(2.08	-2.67)	0.61	(0.47	-0.81)	1.91	(1	-3.65)	2.38	(1.47	-3.84)	-	-	
15-28 days	1.59	(1.44	-1.77)	1.61	(1.41	-1.84)	1.3	(1.08	-1.56)				1.98	(1.25	-3.14)	2.18	(1.07	-4.4
29-56 days	1.53	(1.38	-1.7)	1.89	(1.66	-2.14)	0.7	(0.56	-0.88)	1.73	(1.04	-2.88)	2.22	(1.39	-3.56)	-	-	
> 56 days	1.6	(1.44	-1.76)	1.81	(1.6	-2.04)	1.06	(0.87	-1.29)	1.32	(0.75	-2.35)	0.77	(0.41	-1.46)	5.82	(3.26	-10.3
Washout period																		
1-3 days after Rx.	2.28	(1.96	-2.66)	2.53	(2.11	-3.05)	1.61	(1.19	-2.17)	-	-		-	-		8.76	(4.6	-16.6
4-7 days after Rx.	2.64	(2.28	-3.05)	3.33	(2.82	-3.93)	1.6	(1.19	-2.16)	-	-		3.23	(1.8	-5.8)	-	-	
8-14 days after Rx.	2.31	(2.01	-2.66)	3.26	(2.79	-3.8)	0.64	(0.42	-0.97)	-	-		3	(1.67	-5.38)	-	-	

* Rate ratio was adjusted for age, comorbidity and co-medication in time-varying method.

Appendix1. Incidence rate, age adjusted ratio, and fully adjusted ration of cardiac outcome before and after methylphenidate

	Cardiac Outcome										
Risk Periods	N	Person-years	Incidence rate			Age adjusted rate ratio			Fully adjusted rate ratio		
Composite Cardiac Outcome											
Unexposed	659	2812	2.28	2.2	2.36	1				1	
Exposed	230	744	2.81	2.61	3.03	2.05	1.87	2.24	1.4	1.29	1.52
Times since initiation of methylphenidate											
1-3 days	25	51	4.25	3.75	4.83	3.15	2.76	3.58	2.08	(1.82-	2.39)
4-7 days	27	67	3.5	3.1	3.96	2.59	2.28	2.94	1.72	(1.51-	1.97)
8-14 days	36	107	2.98	2.68	3.31	2.2	1.97	2.46	1.48	(1.32-	1.67)
15-28 days	42	147	2.54	2.3	2.8	1.88	1.69	2.09	1.28	(1.14-	1.43)
29-56 days	40	146	2.46	2.22	2.73	1.82	1.63	2.03	1.24	(1.1-	1.39)
> 56 days	60	225	2.51	2.29	2.76	1.86	1.68	2.06	1.3	(1.17-	1.45)
Arrhythmias											
Unexposed	414	1797	1.25	1.19	1.32	1			1		
Exposed	163	511	2.88	2.63	3.15	2.22	1.98	2.48	1.56	1.41	1.72
Times since initiation of methylphenidate											
1-3 days	20	36	4.78	4.15	5.51	3.81	3.29	4.42	2.56	2.19	3
4-7 days	19	47	3.47	3	4.01	2.76	2.38	3.21	1.87	1.59	2.19
8-14 days	28	74	3.27	2.89	3.69	2.6	2.29	2.96	1.79	1.56	2.05
15-28 days	26	102	2.22	1.96	2.52	1.77	1.55	2.02	1.23	1.07	1.41
29-56 days	29	98	2.6	2.31	2.94	2.08	1.82	2.36	1.45	1.27	1.67
> 56 days	41	155	2.46	2.19	2.75	1.96	1.73	2.22	1.4	1.23	1.6
Hypertensive disease											
Unexposed	191	797	2.75	2.58	2.93	1			1		

Exposed	57	195	2.52	2.15	2.95	1.63	1.36	1.95	0.99	0.85	1.17
Times since initiation of methylphenidate											
1-3 days	6	13	3.79	2.93	4.9	2.42	1.86	3.15	1.45	1.1	1.91
4-7 days	9	18	4.32	3.49	5.35	2.76	2.21	3.43	1.63	1.3	2.06
8-14 days	5	28	1.51	1.14	2	0.97	0.72	1.29	0.57	0.42	0.77
15-28 days	14	40	3.04	2.54	3.63	1.94	1.61	2.34	1.2	0.98	1.46
29-56 days	8	41	1.72	1.37	2.16	1.1	0.87	1.39	0.65	0.51	0.83
> 56 days	15	55	2.45	2.03	2.95	1.56	1.28	1.91	0.99	0.8	1.23
Myocardial Infarction											
Unexposed	29	111	0.91	0	.	1			1		
Exposed	5	25	1.64	0.97	2.76	1.08	0.59	1.97	0.75	0.45	1.26
Times since initiation of methylphenidate											
1-3 days	0	1	0	0	.	0	0	.	0	0	.
4-7 days	0	2	0	0	.	0	0	.	0	0	.
8-14 days	1	3	3.13	1.79	5.48	2	1.11	3.6	1.45	0.72	2.94
15-28 days	0	5	0	0	.	0	0	.	0	0	.
29-56 days	2	6	2.9	1.88	4.47	1.85	1.16	2.97	1.27	0.73	2.21
> 56 days	2	8	2.22	1.38	3.57	1.42	0.84	2.4	0.98	0.53	1.82
Stroke											
Unexposed	27	109	1.64	1.38	1.95	1			1		
Exposed	7	27	2.75	1.85	4.09	1.87	1.14	3.06	1.21	0.78	1.86
Times since initiation of methylphenidate											
1-3 days	0	2	0	0	.	0	0	.	0	0	.
4-7 days	0	2	0	0	.	0	0	.	0	0	.
8-14 days	2	4	6.09	3.95	9.39	3.71	2.31	5.97	1.99	1.17	3.38
15-28 days	2	5	4.66	3	7.23	2.84	1.76	4.6	1.67	1	2.78

29-56 days	2	5	4.28	2.73	6.7	2.61	1.6	4.27	1.88	1.12	3.17
> 56 days	1	9	1.4	0.75	2.62	0.85	0.44	1.67	0.65	0.32	1.32
Heart Failure											
Unexposed	20	80	0.09	0		1			1		
Exposed	4	16	2.53	1.42	4.52	1.16	0.59	2.29	1.03	0.59	1.78
Times since initiation of methylphenidate											
1-3 days	0	1	0	0	.	0	0	.	0	0	.
4-7 days	0	1	0	0	.	0	0	.	0	0	.
8-14 days	0	2	0	0	.	0	0	.	0	0	.
15-28 days	1	3	4.07	2.23	7.41	1.92	1.02	3.59	1.59	0.75	3.35
29-56 days	0	3	0	0	.	0	0	.	0	0	.
> 56 days	3	7	6.9	4.29	11.1	3.25	1.89	5.59	4.39	2.4	8.02

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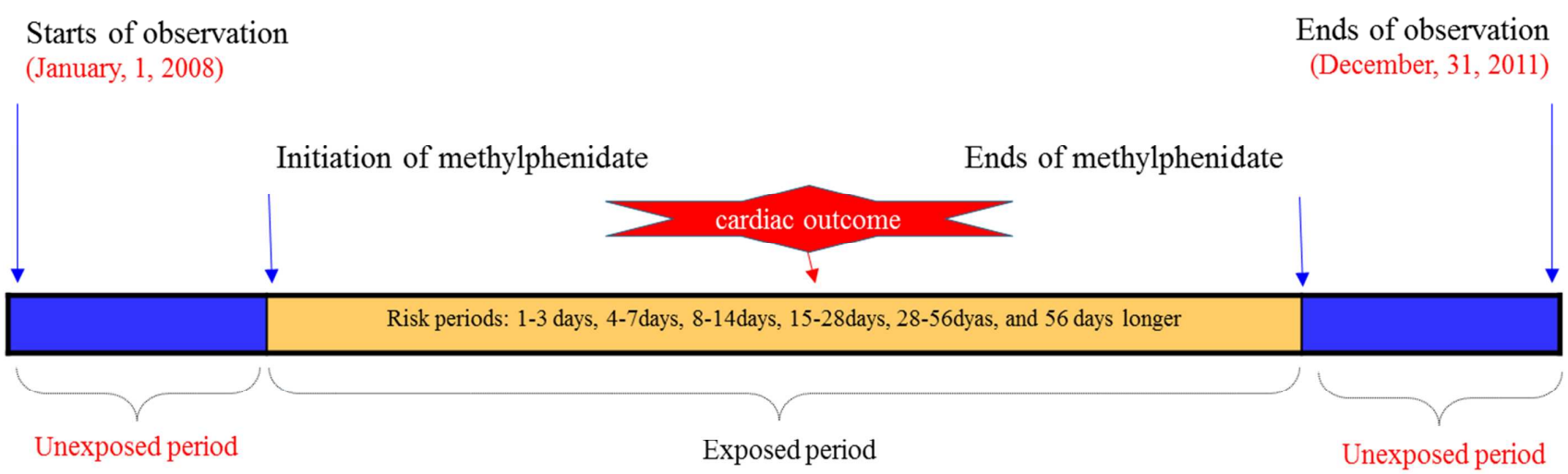

Figure1. Self-controlled case series study