Association between methylphenidate and risk of myocardial infarction: a multinational self-controlled case series study

Running title: Methylphenidate and risk of myocardial infarction

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Abstract

Purpose: To investigate the association between use of methylphenidate and risk of myocardial infarction among Asians.

Methods: We conducted a multinational self-controlled case series study using nationwide healthcare databases of South Korea (2002-2018), Taiwan (2004-2015), and Hong Kong (2001-2016). Of patients with myocardial infarction who were also prescribed methylphenidate within the observation period, methylphenidate use was classified into four mutually exclusive periods by each person-day: exposed (exposed to methylphenidate), pre-exposure (prior to the first methylphenidate prescription), washout (after the end of methylphenidate treatment), and baseline (unexposed to methylphenidate). Risk of myocardial infarction among the three periods of methylphenidate use was compared to the baseline period using conditional Poisson regression analysis to estimate incidence rate ratios (IRRs) with 95% confidence intervals (CIs).

Results: We identified 2104, 484, and 30 patients from South Korea, Taiwan, and Hong Kong, respectively. Risk of myocardial infarction was the highest during the pre-exposure period in all three populations: South Korea, pre-exposure (IRR 3.17, 95% CI 3.04-3.32), exposed (1.05, 1.00-1.11), washout (1.92, 1.80-2.04); Taiwan, pre-exposure (1.97, 1.78-2.17), exposed (0.72, 0.65-0.80), washout (0.56, 0.46-0.68); Hong Kong, pre-exposure (18.09, 8.19-39.96), exposed (9.32, 3.44-25.28), washout (7.69, 1.72-34.41). Following stratification for age and sex, the trends remained analogous to the main findings across all three populations.

Conclusions: Although a positive association between initiating methylphenidate and the onset of myocardial infarction was observed, the risk was the highest in the period before its initiation. Thus, this multinational study suggests there was no causal relationship between methylphenidate and myocardial infarction among Asians.

Keywords: methylphenidate, myocardial infarction, multinational study, self-controlled case series, Asian population

Key Points

- Risk of myocardial infarction was already elevated prior to initiating treatment with methylphenidate.
- Initiating treatment with methylphenidate was not associated with the onset of myocardial infarction among Asians across all ages.
- Findings from this study suggests there is no evidence to support the hypothesis that methylphenidate use triggers the onset of myocardial infarction.

Introduction

Methylphenidate is a stimulant that is widely prescribed to treat attention-deficit hyperactivity disorder (ADHD) and is effective at reducing core ADHD symptoms.[1, 2] Besides ADHD, methylphenidate is also prescribed to patients with neurological disorders or cancer for rehabilitation or palliative purposes, respectively.[3-6] Owing to its various uses, there is a trend of increased methylphenidate use across all ages.[2] However, concerns of myocardial infarction following its use continue to be debated[7-9] with case reports reported for children/adolescents,[10, 11] adults,[12-16] and the elderly.[17] Although the mechanism for an association has yet to be elucidated, the risk of myocardial infarction may be due to the cardiopressor dopaminergic/noradrenergic effects of methylphenidate that result in increased heart rate and blood pressure.[18, 19]

Despite this increasing therapeutic use of methylphenidate across the lifespan, no study has comprehensively evaluated the risk of myocardial infarction associated with its use in all ages. The few studies that assessed this association in children/adolescents lacked statistical power and did not reach statistical significance. A self-controlled case series study of 52 patients reported an incidence rate ratio (IRR) of 1.33 (95% confidence interval [CI] 0.90-1.98),[20] while one cohort study found no myocardial infarction events among ADHD drug users.[21] Two cohort studies of adults/elderly found similar inconclusive results (hazard ratio [HR] 0.89, 95% CI 0.71-1.13;[22] 0.87, 0.63-1.21),[23] where only one study included the elderly.[23] Despite Asians having comparable myocardial infarction risks to Caucasians,[24] no formal assessment was done in this ethnic population as previous studies primarily focused on Caucasians.[21-23, 25] Moreover, the risk of myocardial infarction associated with methylphenidate in all ages is yet to be examined although its risk is known to differ among children and adults. Also, prior studies were unable to examine the temporal association

between methylphenidate use and the onset of myocardial infarction by making between-person comparisons.

Thus, we aimed to assess the association between methylphenidate use and the risk of myocardial infarction by conducting a multinational self-controlled case series study that makes within-person comparisons among Asians.

Materials and Methods

Participating Data Sources

We used a distributed network approach and applied a common data model (CDM) specific to our study (Table S1 and Fig S1).[26-28] Researchers from each site converted their original data structure to fit the CDM prior to conducting the analyses. Then, according to the pre-specified study protocol, the coordinating centre (South Korea; hereafter Korea) created a single syntax that was distributed to each site and the analyses conducted at the sites. Finally, the analysis results were returned to the coordinating centre for collation.

Participating data sources were 1) Korea's National Health Insurance Service-National Health Insurance Database (2002-2018),[29] 2) Taiwan's National Health Insurance Database (2004-2015),[30] and 3) Hong Kong's Clinical Data Analysis and Reporting System database (2001-2016).[31] Detailed explanation of each database is described in Table S2. The study received ethical approval by the institutional review board of each site (Korea: SKKU 2018-03-009; Taiwan: B-ER-107-012; Hong Kong: UW12-136).

Self-controlled Case Series Design

We used the self-controlled case series design to investigate our study objectives and deemed this design most appropriate as methylphenidate use is transient and myocardial infarction is an acute event.[32, 33] This design uses only those who experienced both the

exposure and outcome of interest within the observation period and is bi-directional in that, patients are observed both before and after an event. Moreover, this design allows for the implicit control of measured and unmeasured time-invariant confounders by making within-person comparisons.[32] The main effect estimate is the IRR, which is estimated by dividing the outcome incidence rate during periods of exposure by that of in periods of no exposure. A visual representation of our study is shown in Fig 1.

Study Population

Of 50 million inhabitants from Korea, 23 million inhabitants from Taiwan, and 7 million inhabitants from Hong Kong, we identified all patients with myocardial infarction who were also prescribed methylphenidate within the observation period (Table S1). We excluded those diagnosed with myocardial infarction or prescribed methylphenidate in the first year of our observation period (2002 for Korea, 2004 for Taiwan, 2001 for Hong Kong) to restrict to patients with an incident diagnosis and prescription. Furthermore, we excluded patients who died within our observation period to comply with the design's key assumption,[32] and further, all those with an equal date of myocardial infarction diagnosis and methylphenidate prescription as causal associations were unable to be determined. As we aimed to assess the association between methylphenidate use and myocardial infarction, all methylphenidate users were included, regardless of the presence of an ADHD diagnosis (Fig 2).

Exposure Assessment

All formulations (standard and extended-release) and dose strengths of methylphenidate were included. Exposure to methylphenidate was assessed as time-varying using the date of prescription and the days' supply obtained from each participating database

(Table S1). Person-time of exposed periods (days) was divided into 1-7, 8-14, 15-28, 29-56, and >56 after initiating methylphenidate. Subjects contributed to consecutive periods when they were continuously exposed to methylphenidate (next prescription continued without disturbance from its previous). Moreover, as patients on methylphenidate sometimes have drug holidays, it is not uncommon for there to be treatment gaps throughout the observation period. For this reason, person-time after discontinuation were not classified as new treatments, and instead classified into the >56 days category of the exposed period.

We also defined two consecutive 30-day pre-exposure periods prior to the first date of methylphenidate treatment. These periods accounted for the possibility that the occurrence of myocardial infarction could influence the probability of subsequent methylphenidate treatment. Finally, three consecutive washout periods of 1-7, 8-14, and 15-28 days after the end date of methylphenidate treatment were included as patients may not take the medication strictly according to the instructions given. All remaining person-time was considered as baseline (unexposed) periods.

Outcome Definition

Our outcome of interest was acute myocardial infarction, defined using primary or secondary diagnosis records from any healthcare setting (Table S1). If a patient had multiple diagnoses of myocardial infarction, we included only the first event to avoid any potential bias arising from the second event being influenced by the first event.[32]

Potential Confounders

We included the following time-variant confounders: age, comorbidities, and co-medication use (Table S1). Age was assessed on the date of the first methylphenidate prescription and comorbidities and co-medications were assessed throughout the period of

follow-up. Atomoxetine, a non-stimulant treatment for ADHD, is approved in the three study countries only for secondary treatment and was therefore, not included in our study. Amphetamine-based medications are not available for prescription in these countries.

Statistical Analysis

We described the patient's baseline characteristics using counts (proportions) for categorical variables and mean (standard deviation [SD]) for continuous variables. We calculated the incidence rate per 100 person-years of myocardial infarction and the adjusted IRRs with 95% CIs for the risk of myocardial infarction in the exposed, pre-exposure, and washout periods of methylphenidate use compared to the baseline period using conditional Poisson regression analysis, adjusting for all time-variant confounders aforementioned. We also conducted further analysis using the spline-based interpolation self-controlled case series to observe the risk of myocardial infarction before and after the initiation of methylphenidate treatment.[34]

We stratified on sex, age group (children/adolescent [6-19 years], young adults [20-47 years], middle-aged adults [48-64 years], geriatrics [≥65 years]), and those with a prior history of traumatic brain injury, stroke, and cancer throughout the observation period.

We conducted sensitivity analyses by changing the reference exposure period to the 31-60 day pre-exposure period to directly compare the risk between the exposed and pre-exposure period. All analyses were conducted using SAS statistical software (SAS Institute Inc., Cary, NC, USA) and Python software version 3.7.5 (Python Software Foundation, Wilmington, NC, USA) with a two-sided *p*-value <0.05 considered statistically significant.

Results

We identified 2,104 patients from Korea, 484 patients from Taiwan, and 30 patients from Hong Kong (Fig 2); of these, the majority were aged ≥65 years (Korea 42%, Taiwan 55%, Hong Kong 73%). The mean age at incident methylphenidate prescription was 57.7 (SD 18.8 years), 64.9 (15.8), and 69.9 (19.2) years in Korea, Taiwan and Hong Kong, respectively. Baseline clinical characteristics of comorbidities and use of co-medications between the three populations were similar in proportions (Table 1).

The incidence rate per 100 person-years of myocardial infarction during the exposed period was 0.07 (95% CI 0.07-0.08), 0.11 (0.10-0.13), and 0.51 (0.22-1.23) in Korea, Taiwan, and Hong Kong, respectively. An elevated risk of myocardial infarction was found in the three periods of methylphenidate use (exposed, pre-exposure, washout) compared to the baseline period, with the risk being highest in the pre-exposure period in all populations: Korea, pre-exposure (IRR 3.17, 95% CI 3.04-3.32), exposed (1.05, 1.00-1.11), washout (1.92, 1.80-2.04); Taiwan, pre-exposure (1.97, 1.78-2.17), exposed (0.72, 0.65-0.80), washout (0.56, 0.46-0.68); Hong Kong, pre-exposure (18.09, 8.19-39.96), exposed (9.32, 3.44-25.28), washout (7.69, 1.72-34.41) (Table 2). Analysis using the spline-based interpolation self-controlled case series showed that the incidence rate of myocardial infarction increased significantly before the initiation of methylphenidate treatment and reached a peak before its initiation (Fig 3).

After stratifying for age, sex, history of cancer or traumatic brain injury, analogous trends to the main findings were observed (Table S3 and Table S4). Our main findings remained consistent with sensitivity analyses that set the pre-exposure period as the reference period as there was no increased risk, implying that methylphenidate treatment does not trigger an additional risk of myocardial infarction (Table S5).

Discussion

In this multinational study of Korea, Taiwan, and Hong Kong, we examined the risk of myocardial infarction associated with methylphenidate. The risk of myocardial infarction was consistently elevated in the period prior to initiating methylphenidate treatment in all three populations and decreased in the period of exposure to methylphenidate and in the period after the end of methylphenidate treatment. While the risks were lower in the exposed and washout periods compared to that of the pre-exposure period, the IRRs were greater than one (with the 95% CI excluding the null) in Korea and Hong Kong. Thus, this is the first study to have demonstrated that the association between methylphenidate use and the onset of myocardial infarction in Asians of all ages is not likely to be causal, despite being positive.

To our knowledge, no published evidence was available on the association between methylphenidate use and the risk of myocardial infarction that encompassed all ages. However, there were few studies done in certain age groups of children/adolescents (aged <19 years) or adults (≥19 years). In comparing our findings to studies conducted in children/adolescents, results were consistent as methylphenidate use was not associated with myocardial infarction.[20, 21, 25] A previous cohort study of children (3-17 years) found a null association between ADHD drug users and risk of myocardial infarction when compared to non-users (HR 0.88, 95% CI 0.16-4.71);[25] a cohort study of children and young adults (2-24 years) failed to provide risk estimates due to nil events of myocardial infarction in ADHD drug users.[21] Moreover, one self-controlled case series study of children/adolescents (≤17 years) found an elevated risk of myocardial infarction, despite being statistically insignificant, in periods prior to methylphenidate use (pre-exposure IRR 1.47, 95% CI 0.83-2.62),[20] which was analogous to our age-stratified analysis. In contrast, one cohort study of children (5-19 years) with ADHD found an increased risk of cardiovascular events associated with stimulant use (HR 2.20, 95% CI 2.15-2.24).[35] However, with myocardial infarction absent from the composite outcome of cardiovascular events (i.e., hypertension, arrhythmia, heart failure,

cerebrovascular diseases and others), this is not directly comparable to our findings. Thus, methylphenidate use appears to not trigger the onset of myocardial infarction in children/adolescents when receiving methylphenidate for ADHD treatment.

We also found consistent null associations between methylphenidate and myocardial infarction among adults or the elderly.[22, 23] Patients included in this multinational study were mainly adults (94.7%), of which, 47.3% were aged ≥65 years. Hence, we believe this age group is likely to have received methylphenidate for mixed purposes[36] such as ADHD, cognitive impairment,[37] revitalizations,[38, 39] or palliative care.[40] Our age-stratified analysis of patients aged ≥20 years also showed that methylphenidate did not trigger myocardial infarction as its incidence rate was already increased in the period prior to initiating methylphenidate. In support, a previous cohort study of adults (25-64 years) found a null association between current methylphenidate use and the risk of myocardial infarction (HR 0.89, 95% CI 0.71-1.13) when compared to non-use.[22] Furthermore, another cohort study of adults (aged >18 years) reported similar null effects when comparing methylphenidate users to non-users for the risk of myocardial infarction (HR 0.87, 95% CI 0.63-1.21) and also among patients aged ≥65 years (1.00, 0.68-1.48).[23] Alongside the evidence that suggests methylphenidate use is not causally associated with myocardial infarction, our findings provide novel real-world evidence in that initiation with methylphenidate treatment does not also trigger the onset of myocardial infarction across all ages.

Our multinational study showed similar trends in the incidence rate of myocardial infarction associated with methylphenidate use in both the main and time-based analyses (Table 2). Our time-based risk analysis showed that although the risk of myocardial infarction was highest in the pre-exposure period, the risk was non-differential in the 1-30 or 31-60 day periods prior to initiating methylphenidate. While this suggests that patients were prescribed methylphenidate after experiencing myocardial infarction and raises potential concerns as

patients with prior history of cardiovascular disease are often considered contraindicated to methylphenidate, results from real-world data suggest that, with careful clinical consideration, methylphenidate can be used safely in these situations. Furthermore, the observed risk could be due to patients undergoing robust checking from their respective physicians prior to initiating methylphenidate treatment, which could have led to opportunistic diagnosis of myocardial infarction. Meanwhile, a moderately increased risk of myocardial infarction was also observed in exposed periods of 15-28 and 29-56 days after initiating methylphenidate. Hence, clinicians should closely monitor their patients for any adverse cardiac events in 2-8 weeks after beginning methylphenidate treatment. Moreover, although an elevated risk was observed in the exposed period, this association was unlikely to be causal as its risk was greater in the pre-exposure period. Finally, unlike Korea and Hong Kong that found increased risk of myocardial infarction in the washout periods, Taiwan showed a reduced risk during this period. Nonetheless, the overall trend of the risk of myocardial infarction declined from its peak in the pre-exposure period to the washout period across the three populations, which are supported by our spline-based self-controlled case series analyses.

This multinational study presents the most comprehensive analysis regarding the association between methylphenidate and myocardial infarction among Asians. Our study has several strengths. First, we used a distributed network approach with a CDM and common statistical analysis program to minimize any source of bias that may have arisen from differences in the data structure or analysis programs; similar results reassure us generalizability. Second, we used the self-controlled case series design to investigate our research objectives. By implicitly controlling for both measured and unmeasured time-invariant confounders such as sex or genetic information, our study is less likely to have been impacted from bias that may arise from unmeasured confounders; this bias has considerable impacts in observational studies that make intra-subject comparisons. Last, our exposure

windows included the periods before and after the end of methylphenidate use to minimize any reverse causality bias. Hence, our findings are believed to be minimally affected by such biases, whereas the observed risk in the pre-exposure period may have not been available for assessment in a cohort study as patients with either the event or exposure of interest before the study period are usually excluded.

Limitations of our study are that, first, there may be heterogeneity in the three healthcare databases used due to discrepancies in the coding system, clinical practice, and cultural differences. However, this is unlikely to have affected our findings as the self-controlled case series analysis implicitly controls for inherent differences among populations. Moreover, although the three databases had representativeness of their entire population, there were distinct differences in the number of patients (Korea 2104; Taiwan 484; Hong Kong 30). However, comparable baseline characteristics and trends in the risk of myocardial infarction associated with methylphenidate were observed between the three populations. Hence, our findings are unlikely to have been affected by heterogeneity within the three databases. Second, there may be outcome misclassification. However, a validation study comparing diagnosis codes from health insurance claims to hospital's electronic medical records found a positive predictive value of 82% in Korea,[41] while that of myocardial infarction in Taiwan and Hong Kong were 88% and 85%, respectively.[42, 43] As there is no reason to suspect a differential rate of outcome misclassification in the methylphenidate exposed and unexposed periods, this is unlikely to have introduced bias in our study. Third, as the self-controlled case series design used in this study only influence acute mechanisms of myocardial infarction, we were unable to examine chronic or long-term effects of myocardial infarction, for instance, change in rate of atherosclerosis, associated with methylphenidate exposure. Last, exposure misclassification is possible as the data used in this study do not provide information on adherence to prescriptions. However, non-compliance is unlikely in

our study as methylphenidate is known to have high persistence rates and we also considered for the possibility where patients may have taken the drug for longer periods by including washout periods. Likewise, misclassification of exposure will not have affected the pre-exposure period as this period is prior to the first date of methylphenidate treatment.

In summary, the incidence rate ratio of myocardial infarction peaked before the start of methylphenidate treatment, remained elevated immediately after the start of treatment, declined during the course of treatment, and peaked again after the end of treatment in an Asian population. Thus, findings from this multinational self-controlled case series study among Asians of all ages do not support the causal association that methylphenidate use triggers the onset of myocardial infarction, despite observing a positive association between methylphenidate and myocardial infarction.

Ethics approval: The study received ethical approval by the institutional review board of each site (South Korea: SKKU 2018-03-009; Taiwan: B-ER-107-012; Hong Kong: UW12-136) and the study complies with the Declaration of Helsinki.

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Availability of data and material: Data used in this study will not be made available to the public due to Data Privacy laws within each respective country that prohibit the sharing of private information with the public.

Code availability: SAS syntax available upon request.

Author Contributions: Mr.Jeong, Mr.Lee, Dr.Lai, and Dr.Man had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

- *Concept and design*: Jeong, Lee, Lai, Man, Wong, Shin.
- *Acquisition, analysis, or interpretation of data*: All authors.
- *Drafting of the manuscript*: Jeong, Lee.
- *Critical revision of the manuscript for important intellectual content*: All authors.
- *Statistical analysis*: Lee, Lai, Liao, Man.
- *Administrative, technical, or material support*: Jeong, Lee.
- *Supervision*: Shin.

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Table 1. Characteristics of patients who were diagnosed with myocardial infarction and prescribed methylphenidate within the study period

	South Korea n=2104 (%)	Taiwan n=484 (%)	Hong Kong n=30 (%)
Duration of methylphenidate exposure (days)			
Median (Q1-Q3)	1019 (797, 1784)	848 (840, 1276)	852 (792, 1509)
Age at first methylphenidate exposure (years)			
Mean ± standard deviation	57.7 ± 18.8	64.9 ± 15.8	69.9 ± 19.2
6-19	131 (6)	7 (1)	‡
20-47	381 (18)	57 (12)	0 (0)
48-64	709 (34)	154 (32)	6 (20)
≥65	883 (42)	266 (55)	22 (73)
Sex			
Male	1077 (51)	310 (64)	15 (50)
Female	1027 (49)	174 (36)	15 (50)
Comorbidities*			
Depressive episode	1447 (69)	244 (50)	‡
Tic disorders	20 (1)	‡	‡
Emotional disorders	15 (1)	‡	0 (0)
Conduct disorders	16 (1)	‡	0 (0)
Manic episode	21 (1)	16 (3)	0 (0)
Bipolar affective disorder	378 (18)	32 (7)	0 (0)
Mental retardation	37 (2)	‡	0 (0)
Hypertension	1707 (81)	429 (88)	0 (0)
Hyperlipidaemia	1596 (76)	374 (77)	0 (0)
Stroke	1130 (54)	321 (66)	0 (0)
Cancer	346 (16)	107 (22)	0 (0)
Traumatic brain injury	428 (20)	131 (27)	0 (0)
Use of co-medications†			
Antipsychotics	1294 (62)	394 (81)	0 (0)
Antidepressants	1935 (92)	382 (79)	0 (0)
Antiepileptics	1671 (79)	357 (74)	‡
Anxiolytics	2051 (98)	474 (98)	0 (0)

Note: Q1, 1st quartile; Q3, 3rd quartile

*Defined as at least one record of diagnosis during the pre-specified observation period

†Defined as co-prescription with methylphenidate during the pre-specified observation period

‡Numbers <5 are not displayed according to confidentiality policies of each participating database

Table 2. Risk of myocardial infarction according to definition of risk period before, during, and after treatment with methylphenidate

	South Korea				Taiwan				Hong Kong			
	IR[†] (95% CI)		IRR[*] (95% CI)		IR[†] (95% CI)		IRR[*] (95% CI)		IR[†] (95% CI)		IRR[*] (95% CI)	
Overall analysis												
Baseline	0.06	(0.06-0.06)	Ref (1.00)		0.08	(0.08-0.08)	Ref (1.00)		0.04	(0.03-0.06)	Ref (1.00)	
Pre-exposure	0.23	(0.22-0.24)	3.17	(3.04-3.32)	0.20	(0.18-0.23)	1.97	(1.78-2.17)	0.79	(0.37-1.70)	18.09	(8.19-39.96)
Exposed	0.07	(0.07-0.08)	1.05	(1.00-1.11)	0.11	(0.10-0.13)	0.72	(0.65-0.80)	0.51	(0.22-1.23)	9.32	(3.44-25.28)
Washout	0.12	(0.11-0.13)	1.92	(1.80-2.04)	0.05	(0.04-0.06)	0.56	(0.46-0.68)	0.35	(0.08-1.60)	7.69	(1.72-34.41)
Pre-exposure (days before start of methylphenidate treatment)												
31 ~ 60	0.23	(0.22-0.25)	3.48	(3.28-3.70)	0.23	(0.20-0.26)	2.03	(1.78-2.31)	0.79	(0.36-1.73)	18.15	(8.31-39.64)
1 ~ 30	0.22	(0.21-0.24)	3.38	(3.18-3.60)	0.18	(0.15-0.21)	1.87	(1.62-2.17)	0.79	(0.36-1.73)	18.15	(8.31-39.64)
Exposed (days after start of methylphenidate treatment)												
1 ~ 7	0.10	(0.09-0.13)	1.05	(0.87-1.27)	NA		NA		NA		NA	
8 ~ 14	0.09	(0.07-0.12)	1.38	(1.11-1.72)	NA		NA		NA		NA	
15 ~ 28	0.09	(0.08-0.11)	1.36	(1.15-1.62)	0.07	(0.04-0.10)	0.39	(0.26-0.57)	1.68	(0.54-5.16)	38.28	(12.79-114.5)
29 ~ 56	0.11	(0.10-0.12)	1.51	(1.33-1.72)	0.19	(0.15-0.24)	1.13	(0.90-1.42)	NA		NA	
>56	0.06	(0.06-0.07)	0.97	(0.92-1.03)	0.14	(0.12-0.16)	1.29	(1.14-1.47)	0.58	(0.27-1.28)	9.57	(3.95-23.17)
Washout (days after end of methylphenidate treatment)												
1 ~ 7	0.13	(0.11-0.14)	2.02	(1.83-2.23)	0.08	(0.06-0.12)	0.98	(0.75-1.29)	NA		NA	
8 ~ 14	0.12	(0.10-0.13)	1.90	(1.69-2.15)	NA		NA		1.38	(0.45-4.24)	30.78	(10.34-91.62)
15 ~ 28	0.11	(0.10-0.12)	1.80	(1.63-1.98)	0.05	(0.04-0.07)	0.63	(0.48-0.82)	NA		NA	

Note: CI, confidence interval; IR, incidence rate; IRR, incidence rate ratio; NA, not applicable

[†]per 100 person-years

[*]Adjusted for time-varying age, comorbidities and co-medications

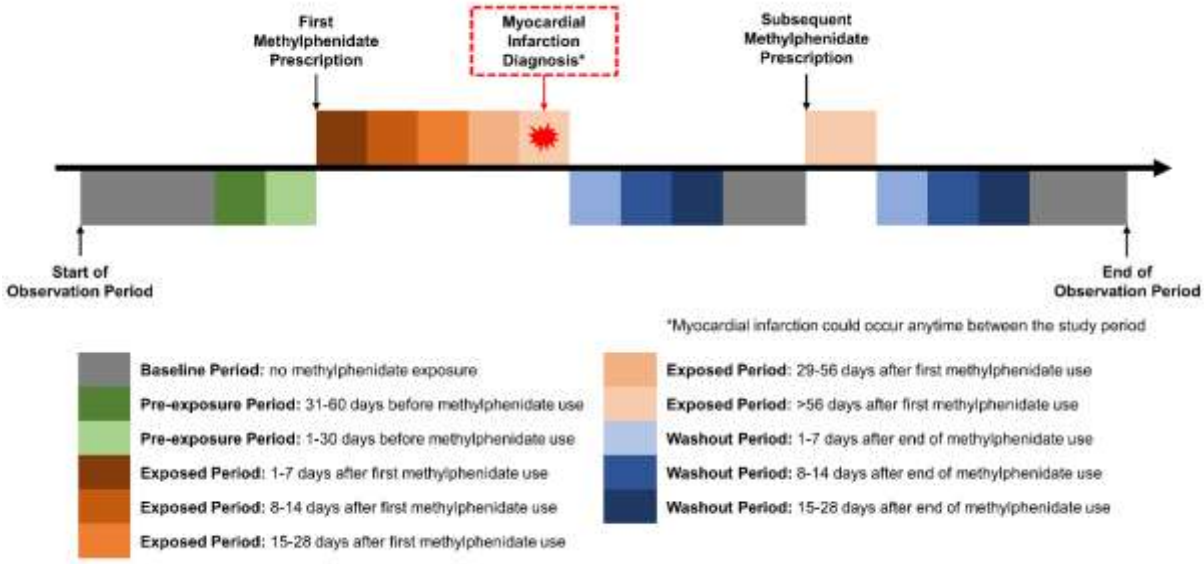
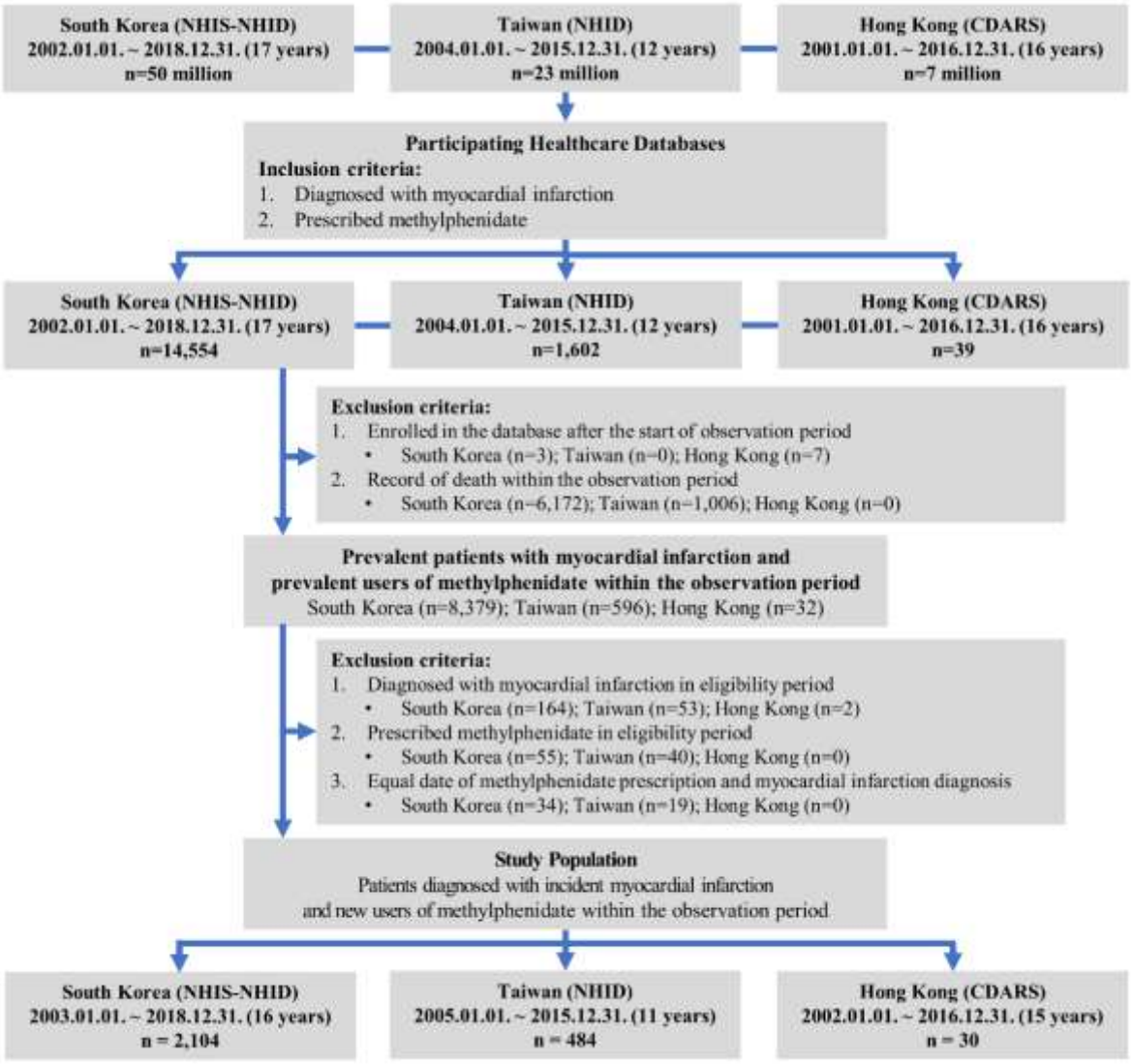
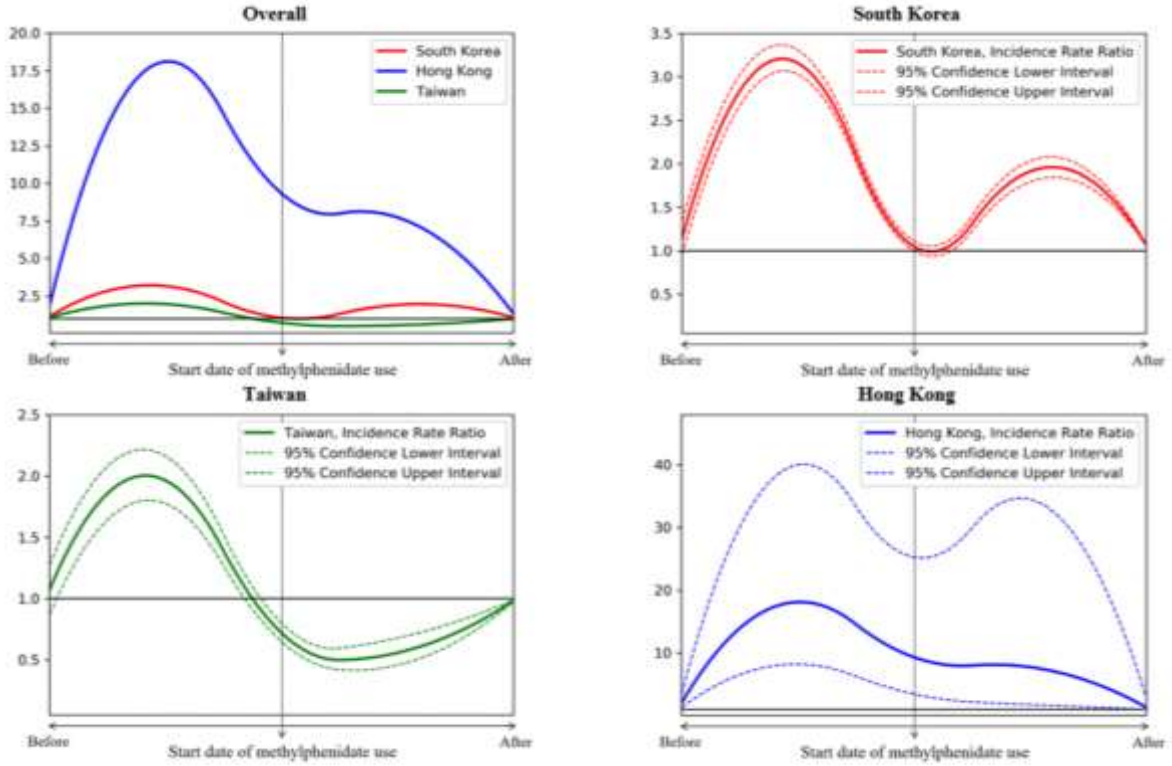


Fig 1. Overview of a timeline for a patient in self-controlled case series study design



Note: CDARS, Clinical Data Analysis and Reporting System; NHID, National Health Insurance Database; NHIS-NHID, National Health Insurance Service-National Health Insurance Database

Fig 2. Flow chart showing the study subject inclusion and exclusion criteria of all participating nations.



*Incidence rate ratio (IRR) of myocardial infarction events throughout the time before and after methylphenidate exposure. The solid line is the estimated IRR, the dashed lines indicate the 95% confidence intervals, and the black line indicates baseline IRR (1.00).

Fig 3. Results from the spline interpolation self-controlled case series analysis

Supporting Information

Figure S1. Overview of the distributed network and common data model approach with the data structure shown after conversion to the common data model

Table S1. Diagnosis and drug code mapping of comorbidities and comedications included in the study

Table S2. Participating databases

Table S3. Sex- and age-stratified analysis of the risk of myocardial infarction according to definition of risk period before, during, and after treatment with methylphenidate

Table S4. Subgroup analysis of the risk of myocardial infarction associated with methylphenidate treatment among patients with history of stroke, cancer, and traumatic brain injury

Table S5. Sensitivity analysis of the risk of myocardial infarction according to definition of risk period before, during, and after treatment with methylphenidate, when compared to the pre-exposure period

Table S1. Diagnosis and drug code mapping of comorbidities and comedications included in the study

	South Korea NHIS-NHID	Taiwan NHID	Hong Kong CDARS
Diagnosis	**ICD-10**	**ICD-9-CM**	
Outcome of Interest			
Myocardial infarction	I21	410	
Comorbidities			
Depressive episode	F32-F33	296.2-296.3, 300.4, 311	
Tic disorders	F95	307.2	
Emotional disorders with onset specific to childhood	F93	313	
Conduct disorders	F91	312.0-312.2	
Manic episodes	F30	296.0, 296.1, 296.81	
Bipolar affective disorders	F31	296.4-296.7, 296.80, 296.89	
Mental retardation	F70-F79	317-319	
Hypertension	I10-I15	401-405	
Hyperlipidaemia	E78	272	
Stroke	I60-I64	430-436	
Cancer	C00-C99	140-209	
Traumatic brain injury	S02.0, S02.1, S02.8, S02.9, S06.0-S06.9	800-804, 850-854	
Drug	**NDC code**	**ATC code**	
Study Drug			
Methylphenidate		N06BA04	N06BA04
Co-medications			
Antipsychotics	**For internal use in South Korea**	N05A	N05A
Antidepressants		N06A	N06A
Anxiolytics		N05B	N05B
Antiepileptics		N03A	N03A

Note: ATC, Anatomical Therapeutic Chemical; CDARS, Clinical Data Analysis and Reporting System; ICD-9-CM, International Classification of Disease 9th Revision-Clinical Modification; ICD-10, International Classification of Disease 10th Revision; NDC, National Drug Chemical, NHIS-NHID, National Health Insurance Service- National Health Insurance Database; NHID, National Health Insurance Database

Table S2. Participating databases

South Korea's National Health Insurance Service-National Health Insurance Database (2002-2018)
The South Korean National Health Insurance Service-National Health Insurance Database (NHIS-NHID) has been widely used in for pharmacoepidemiology research. Korea's national health insurance program was initiated in 1977 and achieved universal coverage of the entire population by 1989. The NHIS-NHID contains all information on diagnoses and prescribed drugs for about 50 million Koreans. The NHIS-NHID includes an anonymized identifier representing each individual together with age, sex, diagnoses, and prescription drugs. Information on prescribed drugs includes generic name, prescription date, duration, and route of administration. In particular, the NHIS-NHID includes all prescription information from both in- and outpatient settings, owing to a fee-for-service system. All diagnoses are coded according to ICD-10. Previous validation studies have compared the diagnoses derived from the claims database with the ideal of actual diagnoses recorded in the patients' medical records obtained from hospital or clinic chart review. The overall positive predictive value of all diagnoses was about 82%.
Taiwan's National Health Insurance Database (2004-2015)
Taiwan's National Health Insurance Database (NHID) is maintained and made accessible for research purposes by the National Health Research Institute (NHRI). Taiwan launched a single-payer, mandatory National Health Insurance program, and by 2011, the entire Taiwanese population had been enrolled. The NHRI compiles information on enrollees' demographics, healthcare professionals and facilities, claims from inpatient and ambulatory care, and contracted pharmacies for reimbursement purposes. Personal identities are encrypted for privacy protection, but all data sets can be linked by an unique, anonymous identifiers created by NHRI. All records of reimbursed drugs from inpatient, outpatient, emergency services and contracted pharmacy settings are included.
Hong Kong's Clinical Data Analysis and Reporting System (2001-2016)
The Hong Kong Hospital Authority (HA) is a statutory body that manages all public hospitals and their outpatient clinics in Hong Kong. The HA provides acute hospital care, acute and chronic disease management to patients via outpatient clinics (both specialists and general physicians) throughout Hong Kong (over 7 million people). Data were extracted from the Clinical Data Analysis and Reporting System (CDARS), a database developed by the HA. In 1995, the HA developed the Clinical Management System (CMS), an electronic health record system that allows clinicians to order, document, and review care in their daily practice. The CMS contains patients' data, including demographic information, diagnosis, payment method, prescription information, laboratory tests, and hospital admission and discharge information. Drug information is stored in the system with prescribing details (e.g. drug name, dose, drug frequency). Data from CMS are transferred to CDARS for research and audit purposes. CDARS also contains a multitude of data warehouses, including the Accident and Emergency Information System, Medical Record Abstract System, In-Patient Administration System, and the Pharmacy Management System/Corporate Drug Dispensing History. Patient records in CDARS are anonymous (patient names, Hong Kong identification card numbers, addresses, and telephone numbers are not available) to protect patient confidentiality. A unique patient reference number is generated for each individual case to facilitate data retrieval and further analysis. CDARS has captured data since 1995.

Table S3. Sex- and age-stratified analysis of the risk of myocardial infarction according to definition of risk period before, during, and after treatment with methylphenidate

	South Korea		Taiwan		Hong Kong	
	IRR* (95% CI)		IRR* (95% CI)		IRR* (95% CI)	
Female						
Baseline	Ref (1.00)		Ref (1.00)		Ref (1.00)	
Pre-exposure	2.81	(2.63-3.00)	2.60	(2.25-3.00)	18.48	(5.45-62.63)
Exposed	1.08	(1.01-1.16)	1.33	(1.16-1.53)	21.26	(5.99-75.40)
Washout	1.79	(1.64-1.96)	1.26	(1.01-1.56)	NA	
Male						
Baseline	Ref (1.00)		Ref (1.00)		Ref (1.00)	
Pre-exposure	3.42	(3.21-3.63)	1.68	(1.46-1.92)	16.44	(5.92-45.68)
Exposed	1.03	(0.96-1.11)	0.42	(0.36-0.50)	3.12	(0.64-15.14)
Washout	2.01	(1.84-2.19)	0.23	(0.15-0.34)	12.41	(3.03-50.83)
Aged† 6-19 years						
Baseline	Ref (1.00)		Ref (1.00)		Ref (1.00)	
Pre-exposure	3.14	(2.46-4.00)	20.69	(12.30-34.80)	NA	
Exposed	1.43	(1.19-1.72)	NA		30.30	(<0.00->999.99)
Washout	1.04	(0.76-1.41)	NA		4.73	(<0.00->999.99)
Aged† 20-47 years						
Baseline	Ref (1.00)		Ref (1.00)		Ref (1.00)	
Pre-exposure	3.18	(2.87-3.52)	2.34	(1.72-3.20)	NA	
Exposed	0.70	(0.60-0.80)	0.54	(0.35-0.82)	NA	
Washout	3.22	(2.88-3.59)	NA		NA	
Aged† 48-64 years						
Baseline	Ref (1.00)		Ref (1.00)		Ref (1.00)	
Pre-exposure	3.70	(3.44-3.97)	2.43	(2.05-2.88)	NA	
Exposed	1.38	(1.27-1.50)	0.39	(0.31-0.50)	19.76	(3.29-118.6)
Washout	1.79	(1.60-2.00)	1.23	(0.96-1.57)	NA	
Aged† ≥65 years						
Baseline	Ref (1.00)		Ref (1.00)		Ref (1.00)	
Pre-exposure	2.44	(2.26-2.63)	1.47	(1.27-1.70)	22.90	(9.51-55.14)
Exposed	0.80	(0.74-0.87)	0.97	(0.86-1.10)	5.60	(1.05-29.89)
Washout	1.43	(1.28-1.60)	0.27	(0.18-0.39)	11.17	(2.21-56.49)

Note: CI, confidence interval; IRR, incidence rate ratio; NA, not applicable

*Adjusted for time-varying age, comorbidities and co-medications

†Age at incident methylphenidate exposure

Table S4. Subgroup analysis of the risk of myocardial infarction associated with methylphenidate treatment among patients with history of stroke, cancer, and traumatic brain injury

	South Korea	Taiwan	Hong Kong
	IRR* (95% CI)	**IRR* (95% CI)**	**IRR* (95% CI)**
History of Stroke			
Baseline	Ref (1.00)	Ref (1.00)	Ref (1.00)
Pre-exposure	3.24 (3.06-3.43)	2.15 (1.92-2.41)	NA
Exposed	0.98 (0.92-1.05)	0.81 (0.72-0.92)	NA
Washout	1.54 (1.41-1.70)	0.46 (0.35-0.60)	NA
No History of Stroke			
Baseline	Ref (1.00)	Ref (1.00)	Ref (1.00)
Pre-exposure	3.02 (2.82-3.24)	1.58 (1.28-1.96)	NA
Exposed	1.14 (1.06-1.23)	0.68 (0.55-0.84)	NA
Washout	2.26 (2.08-2.45)	0.77 (0.57-1.04)	NA
History of Traumatic Brain Injury			
Baseline	Ref (1.00)	Ref (1.00)	Ref (1.00)
Pre-exposure	1.57 (1.38-1.79)	1.51 (1.22-1.86)	1.57 (1.38-1.79)
Exposed	0.84 (0.75-0.93)	0.95 (0.80-1.12)	0.84 (0.75-0.93)
Washout	2.10 (1.85-2.38)	0.55 (0.38-0.78)	2.10 (1.85-2.38)
No History of Traumatic Brain Injury			
Baseline	Ref (1.00)	Ref (1.00)	Ref (1.00)
Pre-exposure	3.58 (3.41-3.75)	2.08 (1.86-2.34)	3.58 (3.41-3.75)
Exposed	1.11 (1.05-1.18)	0.62 (0.54-0.72)	1.11 (1.05-1.18)
Washout	1.87 (1.74-2.01)	0.56 (0.44-0.71)	1.87 (1.74-2.01)
History of Cancer			
Baseline	Ref (1.00)	Ref (1.00)	Ref (1.00)
Pre-exposure	1.89 (1.66-2.14)	2.44 (2.03-2.95)	NA
Exposed	0.26 (0.22-0.32)	1.40 (1.18-1.66)	NA
Washout	1.87 (1.62-2.17)	0.84 (0.58-1.21)	NA
No History of Cancer			
Baseline	Ref (1.00)	Ref (1.00)	Ref (1.00)
Pre-exposure	3.41 (3.25-3.58)	1.83 (1.62-2.06)	NA
Exposed	1.23 (1.17-1.30)	0.54 (0.47-0.62)	NA
Washout	1.92 (1.79-2.05)	0.49 (0.39-0.62)	NA

Note: CI, confidence interval; IRR, incidence rate ratio; NA, not applicable
*Adjusted for time-varying age, comorbidities and co-medications

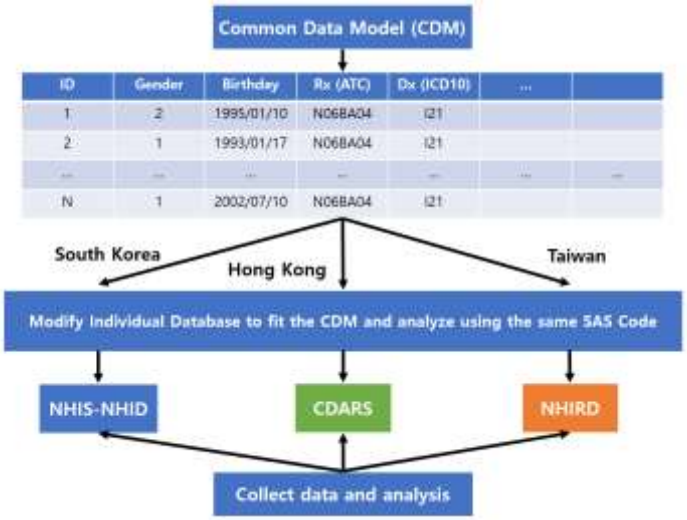
Table S5. Sensitivity analysis of the risk of myocardial infarction according to definition of risk period before, during, and after treatment with methylphenidate, when compared to the pre-exposure period

	South Korea		Taiwan		Hong Kong	
	IRR* (95% CI)		IRR* (95% CI)		IRR* (95% CI)	
Overall analysis						
Pre-exposure	Ref (1.00)		Ref (1.00)		Ref (1.00)	
Baseline	0.32	(0.30-0.33)	0.51	(0.46-0.56)	0.06	(0.02-0.14)
Exposed	0.33	(0.31-0.35)	0.37	(0.32-0.42)	0.52	(0.16-1.70)
Washout	0.60	(0.56-0.65)	0.29	(0.23-0.36)	0.43	(0.08-2.18)
Baseline (no exposure-methylphenidate treatment)						
	0.32	(0.30-0.34)	0.53	(0.46-0.62)	0.06	(0.03-0.12)
Pre-exposure (days before start of methylphenidate treatment)						
1 ~ 30	1.04	(0.95-1.13)	1.08	(0.89-1.32)	1.00	(0.33-3.03)
Exposed (days after start of methylphenidate treatment)						
1 ~ 7	0.31	(0.25-0.37)	NA		NA	
8 ~ 14	0.40	(0.32-0.50)	NA		NA	
15 ~ 28	0.41	(0.34-0.49)	0.21	(0.14-0.31)	2.11	(0.57-7.78)
29 ~ 56	0.47	(0.41-0.54)	0.61	(0.46-0.79)	NA	
>56	0.31	(0.29-0.34)	0.69	(0.57-0.84)	0.53	(0.17-1.64)
Washout (days after end of methylphenidate treatment)						
1 ~ 7	0.67	(0.60-0.75)	0.53	(0.39-0.72)	NA	
8 ~ 14	0.62	(0.54-0.70)	NA		1.70	(0.46-6.23)
15 ~ 28	0.57	(0.51-0.64)	0.34	(0.25-0.46)	NA	

Note: CI, confidence interval; IRR, incidence rate ratio; NA, not applicable

*Adjusted for time-varying age, comorbidities and co-medications

Figure S1. Overview of the distributed network and common data model approach with the data structure shown after conversion to the common data model



1. Demographic table

No.	Variable Name	Variable Information	Variable Format	Details
1.	pid	Unique patient identifier	Numeric or Character	
2.	bdt	Variable to identify the date of birth	Numeric; Date, yymmdd10.	
3.	ddt	Variable to identify the date of death	Numeric; Date, yymmdd10.	
4.	sex	Variable to identify the sex	Numeric	F: 0; M: 1; Missing: 9
5.	enroll_in_dt	Variable to identify the date of insurance enrolment	Numeric; Date, yymmdd10.	
6.	enroll_out_dt	Variable to identify the date of insurance exit	Numeric; Date, yymmdd10.	

2. Drug table

No.	Variable Name	Variable Information	Variable Format	Details
1.	pid	Unique patient identifier	Numeric or Character	
2.	rxstt	Variable to identify the start date of drug supply	Numeric; Date, yymmdd10.	
3.	rxend	Variable to identify the end date of drug supply	Numeric; Date, yymmdd10.	
4.	rxday	Variable to identify the days of drug supply	Numeric	
5.	rxcd	Variable to identify the drug code	Character	ATC code
6.	rxunit	Variable to identify the dose unit of drug supply	Numeric	
7.	rxquan	Variable to identify the quantity of drug supply per 1 dose	Numeric	e.x., 1 = 1 tablet
8.	rxfreq	Variable to identify the frequency of drug supply per 1 day	Numeric	e.x., 1 = 1 supply/day
9.	setting	Variable to identify the route of drug supply	Character	Inpatient: IP, Outpatient: OP

3. Diagnosis table

No.	Variable Name	Variable Information	Variable Format	Details
1.	pid	Unique patient identifier	Numeric or Character	
2.	dxstt	Variable to identify the date of diagnosis code received	Numeric; Date, yymmdd10.	
3.	dxcd	Variable to identify the diagnosis code	Character	ICD-10 or ICD-9-CM code
4.	setting	Variable to identify the route of diagnosis code received	Character	Inpatient: IP, Outpatient: OP

Example Data set

Demographic table

pid	sex	bdt	ddt	enroll_in_dt	enroll_out_dt
10001	0	1932-01-08	2013-08-13	1932-01-08	2013-08-13
10092	1	1988-08-08	.	1988-08-08	
10100	0	1991-08-21	.	1991-08-21	

Drug table

pid	rxstt	rxend	rxday	rxcd	rxunit	rxquan	rxfreq	setting
10001	2013-08-01	2013-08-07	7	N06BA04	10	1	3	IP
10001	2013-09-01	2013-09-29	28	N06BA04	5	3	3	IP
10001	2014-10-12	2014-10-18	7	N06BA04	28	2	1	OP

Diagnosis table

pid	dxstt	dxcd (ICD-10)	setting

10001	2006-03-21	I21	IP
10002	2010-02-17	I21	OP
10003	2013-01-08	F90	OP