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Original Article

Cardiovascular and Metabolic Risk of Antipsychotics in Children and Young Adults: A Multinational Self-Controlled Case Series Study

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Abstract

Aims:

The risk of antipsychotic-associated cardiovascular and metabolic events may differ among countries, and limited real-world evidence has been available comparing the corresponding risks among children and young adults. We therefore evaluated the risks of cardiovascular and metabolic events in children and young adults receiving antipsychotics.

Methods:

We conducted a multinational self-controlled case series (SCCS) study and included patients aged 6-30 years old who had both exposure to antipsychotics and study outcomes from four nationwide databases of Taiwan (2004-2013), Korea (2011-2016), Hong Kong (2001-2014), and the UK (1997-2016) that covers a total of approximately 100 million individuals. We investigated three antipsychotics exposure windows (i.e., 90 days pre-exposure, 1-30 days, 30-90 days, and 90+ days of exposure). The outcomes were cardiovascular events (stroke, ischemic heart disease, and acute myocardial infarction), or metabolic events (hypertension, type 2 diabetes mellitus, and dyslipidemia).

Results:

We included a total of 48,515 individuals in the SCCS analysis. We found an increased risk of metabolic events only in the risk window with more than 90-day exposure, with a pooled IRR of 1.29 (95%CI: 1.20-1.38). The pooled IRR was 0.98 (0.90-1.06) for 1-30 days and 0.88 (0.76-1.02) for 31-90 days. We found no association in any exposure window for cardiovascular events. The pooled IRR was 1.86 (0.74-4.64) for 1-30 days, 1.35 (0.74-2.47) for 31-90 days, and 1.29 (0.98-1.70) for 90+ days.

Conclusions:

Long-term exposure to antipsychotics was associated with an increased risk of metabolic events but did not trigger cardiovascular events in children and young adults.

Keywords: antipsychotics; cardiovascular events; metabolic syndrome; children and young adults; multi-national study; self-controlled case series

INTRODUCTION

The average prevalence of psychiatric disorders was about 22.1% with the severe disorders (schizophrenia, bipolar disorder, severe depression, severe anxiety, and severe post-traumatic stress disorder) estimated to be 5.1%.(Charlson et al., 2019) In children, the prevalence has been reported to be about 6.7% but varies between different countries.(Erskine et al., 2017) The use of antipsychotics has increased over the years and has become one of the mainstays for the treatment of psychiatric disorders in children, despite lingering concerns over side effects.(Harrison et al., 2012, Lao et al., 2017, Lee et al., 2018) Specifically, in such young populations, antipsychotic medications may induce cardiovascular and metabolic abnormalities (such as obesity, hyperglycemia, dyslipidemia, and diabetes mellitus) that could affect their physical, mental, and social development.(Hsu et al., 2013) Moreover, some life-threatening cardiovascular side effects of antipsychotics such as stroke, ischemic heart disease (IHD) and acute myocardial infarction (AMI) have also been reported.(De Hert et al., 2011) Meanwhile, increasing prescribing of antipsychotics is observed among children and young adults,(Olfson et al., 2015) that leads to great concern regarding the safety of antipsychotics.(Pillay et al., 2018) Currently available studies mainly focus on the outcomes of weight change or shifts in metabolic parameters over a short period of time.(Vandenberghe et al., 2018, Sjo et al., 2017) Not much is known about the specific risk of cardiovascular and metabolic events in children and young adults treated with antipsychotics, as previous studies were mainly of small sample size and thus may not have developed sufficient statistical power in their analyses.(Burcu et al., 2018, McIntyre and Jerrell, 2008)

The risk of antipsychotic-associated cardiovascular and metabolic events may differ among countries.(Man et al., 2020) This could potentially be due to variations in healthcare systems and preferences of patients and clinicians in the choice of antipsychotics.(Pillinger et al., 2020) From the genetic perspective, the variant HTR2C gene, which encodes the 5HT2c receptor, may increase metabolic risk, especially by the rs1414334 C allele.(Ma et al., 2014) A survey indicated that this allele is present in a higher proportion of Americans (10%) and Europeans (15%), but, by contrast, is of very low frequency in Asians (1%). This suggests that variations between different ethnicities could affect the risk of cardiovascular and metabolic events.(Mulder et al., 2009) To date, only limited evidence has been available comparing the corresponding risks among children and young adults receiving antipsychotics between different populations in real-world situations. We therefore conducted the current study with four large population-based datasets from Taiwan, Korea, Hong Kong, and the UK, which have

coverage of approximately 100 million individuals in total, to evaluate and benchmark the risk of specific cardiovascular events (stroke, IHD, and AMI) and metabolic events (hypertension, T2DM, and dyslipidemia), associated with antipsychotics in children and young adults.

METHOD

Database Sources

We included databases from Taiwan (Taiwan's National Health Insurance Database; NHID), Korea (Korea's NHID), Hong Kong (Clinical Data Analysis and Reporting System; CDARS), and the UK (The Health Improvement Network; THIN) in this study.(Hsieh et al., 2019, Ilomäki et al., 2020) Additional details about the included databases are presented in **Supplementary Table 1**. We applied a distributed network approach with a common data model (CDM).(Lai et al., 2015) Briefly, the coordination center distributed the common SAS program for analysis, generating aggregated results based on the CDM that standardized the structures and contents of participating databases, and collected the final summary of results from each participating site.(Lai et al., 2015) This approach preserved the confidentiality of the data because the raw data stayed in the local site while the analyses were executed respectively by the sites.(Lai et al., 2018a) Moreover, we could maintain the consistency of analysis among the sites through the use of the common analysis program.(Lai et al., 2018b) The details of the mapping codes for diagnosis and the CDM are presented in **Supplementary Table 2** and **Supplementary Table 3**. The study has been approved by the Human Research Ethics Committee at National Cheng Kung University (No. NCKU HREC-E-105-259-2); the University of Hong Kong/Hospital Authority Hong Kong West Cluster (No. UW15-619); The Health Improvement Network Scientific Review Committee (19THIN087) and the Institutional Review Board of Sungkyunkwan University (SKKU 2018-04-106).

Study Design

We applied a self-controlled case series (SCCS) design to investigate the association between antipsychotics and risk of metabolic/cardiovascular event, whereby the relative risk is estimated based on within-person comparisons rather than between-person comparisons (Petersen et al., 2016, Hallas and Pottegard, 2014). As a result, both measured and unmeasured time-independent confounding factors, such as sex, ethnicity, environmental and cultural factors are eliminated. The design is especially important for multinational study, benchmarking results from different countries with very heterogeneous healthcare conditions.(Lai et al., 2018a)

Source Population and Exposure

We included patients aged 6-30 years diagnosed with mental disorder (ICD-9-CM: 290-319) who were newly receiving oral antipsychotic drugs between 2004-2013 in Taiwan, 2011-

2016 in Korea, 2001-2014 in Hong Kong, and 1997-2016 in the UK. Incident use of antipsychotics was captured based on a one-year washout period before the first record of antipsychotic prescription in the database. We excluded patients who had a record of congenital disorders, including congenital heart disease, familial hypercholesterolemia, and type 1 diabetes. We also excluded patients who had a cancer diagnosis record. Details of diagnostic codes are presented in **Supplementary Table 3.**

Case Identification and Ascertainments

We included patients who had a record of the outcome of interest (cardiovascular events included AMI, IHD, and stroke, and metabolic events included hypertension, dyslipidemia, and T2DM) for the analyses. To improve the validity of diagnoses of metabolic events, we confirmed cases by the records for corresponding drug prescriptions, including oral hypoglycemic agents (A10B) for T2DM, lipid-modifying agents (C10) for dyslipidemia, and antihypertensive drugs including diuretics (C03A and C03B), beta-blockers (C07, except propranolol; C07AA05), calcium channel blockers (C08CA) and angiotensin-converting enzyme inhibitors (ACEI) / angiotensin receptor blockers (ARB) (C09).

Definition of Risk Periods

We defined the observation period based on the availability of data sources as mentioned in the previous section. Observational periods began on the first available date in the corresponding database, or the sixth birthday of the patient (whichever was later) and ended on the last available date in the corresponding database, the 31st birthday of the patient, or registered date of death (whichever was earlier). For each included participant, we defined the risk periods with respect to the duration of exposure to antipsychotics and categorized them into 5 mutually exclusive windows: (1) 90 days before (pre-exposure), (2) 1-30 days, (3) 31-90 days, (4) more than 90 days of antipsychotics use, and (5) 30-day after the end of antipsychotics use (post-exposure) (**Figure 1)**. Details of ATC codes for antipsychotics are presented in Supplementary Table 4. A pre-exposure period was added to take account of the possibility that the outcome of interest may affect the likelihood of antipsychotics treatment, which in turn may introduce bias into the risk estimate during treatment whereas the post-exposure period acts as a washout period. To manage possible confounding effects due to age, we performed two-year age banding for all patients in the analysis.(Petersen et al., 2016)

Statistical Analysis

We report characteristics of patients included in the analyses by countries and describe

categorical variables (e.g., sex) by number with proportion and continuous variables (e.g., age) by mean with standard deviation (SD). We considered the entire study period and categorized the risk periods in a time-varying manner, i.e. the exposure status was updated according to the treatment time. We calculate incidence rate ratio (IRR) and 95% confidence interval (95% CI) by conditional Poisson regression, adjusted for age in one-year age bands to evaluate the risk of specific cardiovascular and metabolic events associated with antipsychotics in the different risk windows. IRRs for each risk window in each site were pooled by the random-effect model.(DerSimonian and Laird, 1986) The Taiwanese and Korean databases provided a sufficient number of cases to conduct a secondary analysis for the risk comparisons between individual antipsychotics.

RESULTS

Antipsychotic Users from Each Country

We identified a total of 107,425 patients from Taiwan, 284,843 from Korea, 19,034 patients from Hong Kong, and 7,770 patients from the UK. The mean age (±SD) upon receiving the first prescription was 21.1±6.7 years in Taiwan, 23.3±5.3 years in Hong Kong, and 24.9±3.8 years in the UK. We found more males than females in Taiwan (61%), Korea (60%), and the UK (64%), and about the same males and females in Hong Kong **(Table 1).** The patterns and rates of antipsychotics use are presented in **Figure 2.** The proportion of antipsychotics use varied among countries. The most commonly prescribed drugs at initiation were sulpiride in Taiwan, risperidone in Korea, haloperidol in Hong Kong, and olanzapine in the UK.

Pooled Analysis

There were a total of 9730 (overall incidence rate, 11.5 per 100 person-years), 38432 (12.4 per 100 person-years), 233 (7.6 per 100 person-years), and 120 (11.9 per 100 person-years) patients with at least one record of cardiovascular or metabolic events in Taiwan, Korea, Hong Kong, and the UK, respectively. An increased risk of metabolic events was observed with more than 90-days of antipsychotics exposure with the pooled IRR of 1.29 (95% CI: 1.20-1.38), but not in other risk windows. The corresponding IRR was 0.98 (95%CI: 0.90-1.06) for 1-30 days and 0.88 (0.76-1.02) for 31-90 days of antipsychotics exposure. The I^2 for heterogeneity ranged from 0%-39.5% in the pooled estimates from metabolic events. For cardiovascular events, no significant association was identified in any risk windows in the pooled analysis. The pooled IRR was 1.86 (0.74-4.64) for 1-30 days, 1.35 (0.74-2.47) for 31-90 days, and 1.29 (0.98-1.70) for more than 90-days of antipsychotics exposure, however, with high heterogeneity (I^2 ranged from 82.4%-98.7%). No significant associations were found in the pre- and post-exposure windows for both outcomes **(Figures 3 and 4).**

Analysis by Sites and Specific Events

The results of SCCS from individual sites varied. We found the risks of metabolic events were higher in the risk period of 90+ days in Taiwan and Korea. The IRR were 1.27 (1.12-1.45) and 1.48 (1.38-1.59) for hypertension, 1.35 (1.12-1.64) and 1.38 (1.28-1.49) for T2DM, and 1.36 (1.20-1.55) and 1.36 (1.28-1.49) for dyslipidemia in Taiwan and Korea, respectively. However, the risk of metabolic events in the period of 90+ days was higher but not reached

statistical significance in Hong Kong and the UK. **(Table 2-1).**

Compared to non-exposure period, we found the risk of stroke to be higher in the pre-exposure period (5.49; 4.72-6.38), 1-30 days (3.51; 3.07-4.01), 31-90 days (2.06; 1.75-2.42), and 90+ days (2.07; 1.77-2.43), and the risk of IHD (1.59; 1.35-1.86) and AMI was higher in the pre-exposure period (6.42; 2.86-14.45) and the risk period of 1-30 days (2.29; 0.91-5.78) in Taiwan **(Table 2-2).** We did not find an association between antipsychotics and cardiovascular events in Korea, except for a higher risk of stroke in the period of 90+ days (1.38; 1.34-1.41) comparing with non-exposure period. In Hong Kong, we found the risk of cardiovascular events, specifically for stroke (5.80; 1.91-17.61) was higher in the risk period of 1-30 days compared to non-exposure period. We did not find any association between the use of antipsychotics and the risk of cardiovascular events in the UK.

DISCUSSION

Previous studies evaluating the safety of antipsychotics in young people were generally with a limited sample size to acquire a precise estimation.(Burcu et al., 2018, McIntyre and Jerrell, 2008) The current study used four large databases from Taiwan, Korea, Hong Kong, and the UK to evaluate the risk of cardiovascular and metabolic events associated with antipsychotics in children, adolescents, and young adults. We identified an increased risk of metabolic events with exposure to antipsychotics for more than 90 days from the pooled results. However, no significant association was found between the use of antipsychotics and the risk of cardiovascular events. This suggested that the increased risk in the metabolic events may not be severe enough to trigger cardiovascular events in children, adolescents, and young adults. Despite the varied risk pattern among countries, the conclusion is consistent with the overall results.

The results of our study were largely consistent with previous studies regarding the association between the risk of metabolic events with antipsychotics use.(Man et al., 2020) However, we found an increased risk of metabolic events only with the antipsychotics exposure for more than 90 days, implicating it may require a period of accumulative exposure of drugs to develop metabolic events. Our pooled analysis did not support the use of antipsychotics was associated with cardiovascular events. However, the finding was based on the results from countries with high heterogeneity. We found an increased risk of cardiovascular events in Taiwan and a specifically higher risk of stroke in Hong Kong in the first 30 days of antipsychotics treatment. In particular, we found patients receiving haloperidol had an increased risk of stroke in the initial stage of treatment in both Taiwan and Hong Kong. Haloperidol has a high affinity for binding to α1 and α2 receptors,(Hensiek and Trimble, 2002) and the blockade of α receptors could cause fluctuations in blood pressure along with some symptoms such as hypotension, hypertension, and QT interval prolongation, leading to a high risk of cardiovascular events.(Cooper et al., 2016, Hiremath et al., 2019) However, a more parsimonious interpretation of this pattern of temporal association is that the observed increased risk of cardiovascular events is not due to antipsychotics but precedes it because an increased risk was also observed in 90 days pre-exposure period from both Taiwan and Hong Kong. The changes in behavioral and mental health symptoms or associated impairment that lead to a medical consultation or comorbidities, which in turn may contribute to the decision to prescribe antipsychotics.

Besides, it is noteworthy that different risk profiles among countries could be attributed to different patterns of antipsychotic or prescribing preferences among the countries. From the study cohorts, we found that SGA use increased over the years in Korea and the UK, and until 2016, SGA accounted for more than 80% of total antipsychotics use in children, adolescents, and young adults. The frequent use of SGA may explain the higher risk of metabolic events within the observation window of more than 90 days after drug initiation, compared to the non-exposure period. We suggest interpreting the results cautiously considering countries' specific situations. For instance, the healthcare accessibility or copayment of medical treatment may be different among countries, leading to various thresholds for seeking medical treatment (Lai et al., 2018b). The possibilities of the capture of events were different among countries. Moreover, the differences in the respective healthcare systems, cultures, behaviors of prescribing, preferences of clinicians among countries may also contribute to the heterogeneity of the results. Therefore we could not make inference on the ethnic differences regarding the adverse effects in our study.

Limitations

We were unable to assess the actual medication adherence of patients, which may cause a bias toward null because patients may or may not be taking the medication. Self-controlled design eliminated time-constant unmeasured confounders, but the results may be influenced by time-variant factors that were not associated age.(Petersen et al., 2016, Hallas and Pottegard, 2014) Protopathic bias should be noted with patients who had undetected cardiovascular events that caused psychosis and the use of antipsychotics. Because clinicians may avoid antipsychotics which are well known to increase metabolic side effects, such as olanzapine for patients with higher baseline risk, the sample size and power of the study may be decreased. On the other hand, because metabolic monitoring is not being implemented routinely in all study countries, we may omit some patients with mild metabolic syndrome.

CONCLUSION

The exposure to antipsychotics for more than 90 days was associated with increased risk of metabolic event, but did not trigger cardiovascular events in children and young adults. Although we found varied risk profiles of cardiovascular and metabolic events between countries, the conclusion remained consistent with the overall results. Nevertheless, clinicians should be mindful of the possible cardiovascular and metabolic risk as with the use of all antipsychotics in children and young adults in clinical practice while long-term use of antipsychotics is required.

Ethics approval: The study has been approved by the Human Research Ethics Committee at National Cheng Kung University (No. NCKU HREC-E-105-259-2); the University of Hong

Kong/Hospital Authority Hong Kong West Cluster (No. UW15-619); The Health Improvement Network Scientific Review Committee (19THIN087) and the Institutional Review Board of Sungkyunkwan University (SKKU 2018-04-106).

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Author Contributions:

Study concept and design: Man, KKC, YC Chang, and ECC Lai.

Data analysis: Su CC and YC Chang.

Interpretation of results: All authors.

First draft of manuscript: ECC Lai.

Review and revise manuscript: All authors.

Conflict of Interest: None.

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Table 1. Baseline characteristics of all antipsychotic users included in the analysis.

	Taiwan	Korea	Hong Kong	The UK
Number of Patients	107,425	284,843	19,034	7,770
Sex, n (%)				
Male	65,532 (61.0)	169,856 (59.6)	9,711 (51.0)	4,956 (63.8)
Female	41,893 (39.0)	114,987 (40.4)	9,323 (49.0)	2,814 (36.2)
Age (mean±SD)	21.1 (±6.7)	19.9 (±6.9)	23.3 (±5.3)	24.9 (±3.8)
Age subgroup, n (%)				
6-12 y	16,091 (15.0)	50,829 (17.8)	667 (3.50)	7 (0.1)
13-18 y	18,986 (17.7)	67,759 (23.8)	3,048 (16.0)	355 (4.6)
19-24 y	32,837 (30.6)	80,726 (28.3)	6,451 (33.9)	3,180 (40.9)
25-30 y	39,511 (36.8)	85,529 (30.3)	8,868 (46.6)	4,228 (54.4)

Table 2-1. Risk of metabolic events among countries.

	Taiwan NHID			Korea NHID			Hong Kong CDARS			UK THIN		
	Events	Person-years	IRR (95% CI)	Events	Person-years	IRR (95% CI)	Events	Person-years	IRR (95% CI)	Events	Person-years	IRR (95% CI)
Metabolic risk												
Baseline	3,898	37,852	1.00 (reference)	20,495	163,759	1.00 (reference)	89	1,581	1.00 (reference)	44	511	1.00 (reference)
Pre-risk (-90 to 0 days)	352	1,207	2.52 (2.25 - 2.82)	1,763	23,396	0.08 (0.04 - 0.19)	5	40	1.40 (0.56 - 3.52)	6	19	2.04 (0.74 - 5.66)
Risk (1-30 days)	437	3,935	1.02 (0.92 - 1.14)	1,980	23,231	0.90 (0.78 - 1.04)	13	137	1.16 (0.62 - 2.17)	10	93	0.79 (0.36 - 1.74)
Risk (31-90 days)	375	3,891	0.81 (0.72 - 0.91)	9,333	54,134	0.98 (0.85 - 1.13)	7	136	0.63 (0.28 - 1.40)	13	92	1.04 (0.50 - 2.16)
Risk (90+ days)	1,130	6,825	1.34 (1.23 - 1.47)	61	5,486	1.21 (1.07 - 1.37)	74	619	0.99 (0.60 - 1.66)	42	240	1.27 (0.69 - 2.33)
Post-risk (1-30 days)	90	838	0.87 (0.70 - 1.07)	447	3,953	0.95 (0.69 - 1.29)	2	23	0.53 (0.12 - 2.27)	1	16	0.34 (0.05 - 2.57)
Risk of hypertension												
Baseline	2,038	19,906	1.00 (reference)	4,886	39,465	1.00 (reference)	45	726	1.00 (reference)	9	92	1.00 (reference)
Pre-risk (-90 to 0 days)	201	623	2.81 (2.42 - 3.26)	11	1,355	0.06 (0.03 - 0.11)	2	18	0.89 (0.21 - 3.75)	3	4	7.72 (1.40 - 42.68)
Risk (1-30 days)	251	1,996	1.16 (1.01 - 1.34)	480	6,172	0.61 (0.56 - 0.68)	9	55	1.41 (0.64 - 3.11)	1	16	0.57 (0.06 - 5.14)
Risk (31-90 days)	209	1,974	0.90 (0.77 - 1.05)	587	6,130	0.72 (0.65 - 0.79)	3	55	0.47 (0.14 - 1.59)	2	16	1.17 (0.21 - 6.60)
Risk (90+ days)	530	3,252	1.27 (1.12 - 1.45)	2,667	14,861	1.48 (1.38 - 1.59)	23	208	0.55 (0.24 - 1.26)	9	38	2.18 (0.53 - 9.03)
Post-risk (1-30 days)	38	427	0.72 (0.52 – 1.00)	118	1,015	0.88 (0.73 - 1.06)	1	10	0.41 (0.05 - 3.24)	0	3	N/A (---- ----)
Risk of type 2 DM												
Baseline	791	7,618	1.00 (reference)	4,154	33,428	1.00 (reference)	37	672	1.00 (reference)	19	208	1.00 (reference)
Pre-risk (-90 to 0 days)	64	254	2.13 (1.64 - 2.77)	11	1,158	0.07 (0.04 - 0.13)	2	18	1.52 (0.35 - 6.65)	2	8	1.34 (0.24 - 7.37)
Risk (1-30 days)	85	867	0.88 (0.69 - 1.11)	422	5,562	0.62 (0.56 - 0.69)	3	73	0.57 (0.17 - 1.96)	5	40	0.94 (0.29 - 3.07)
Risk (31-90 days)	78	857	0.79 (0.61 - 1.01)	389	5,525	0.54 (0.48 - 0.60)	3	73	0.57 (0.17 - 1.97)	7	40	1.34 (0.45 - 3.98)
Risk (90+ days)	286	1,629	1.35 (1.12 - 1.64)	2,441	13,957	1.38 (1.28 - 1.49)	43	338	1.34 (0.65 - 2.76)	17	101	1.08 (0.41 - 2.86)
Post-risk (1-30 days)	22	184	0.86 (0.56 - 1.33)	106	887	0.84 (0.69 - 1.03)	0	12	N/A	0	7	N/A (---- ----)
Risk of dyslipidemia												
Baseline	1,773	17,368	1.00 (reference)	14,562	116,747	1.00 (reference)	12	316	1.00 (reference)	18	230	1.00 (reference)
Pre-risk (-90 to 0 days)	139	563	2.19 (1.83 - 2.61)	45	3,885	0.09 (0.06 - 0.12)	1	7	2.33 (0.27 - 20.11)	1	8	0.92 (0.08 - 10.32)
Risk (1-30 days)	163	1,908	0.78 (0.66 - 0.92)	1,123	16,207	0.56 (0.52 - 0.59)	1	27	0.81 (0.10 - 6.87)	4	40	0.82 (0.23 - 2.94)
Risk (31-90 days)	165	1,887	0.71 (0.60 - 0.85)	1,292	16,091	0.64 (0.61 - 0.68)	1	27	0.82 (0.10 - 6.90)	4	39	0.82 (0.23 - 2.95)
Risk (90+ days)	613	3,534	**1.36 (1.20 - 1.55)**	6,376	37,150	1.38 (1.34 - 1.42)	21	160	2.59 (0.77 - 8.67)	19	110	1.43 (0.56 - 3.63)
Post-risk (1-30 days)	52	399	0.98 (0.74 - 1.30)	303	2,771	0.88 (0.78 - 1.00)	1	4	2.69 (0.25 - 29.41)	1	6	0.81 (0.10 - 6.73)

Abbreviations: National Health Insurance Database, NHID; Clinical Data Analysis and Reporting System, CDARS; The Health Improvement Network, THIN; diabetes mellitus, DM; not available, N/A

Table 2-2. Risk of cardiovascular events among countries.

	Taiwan NHID			Korea NHID			Hong Kong CDARS			UK THIN		
	Events	Person-years	IRR (95% CI)	Events	Person-years	IRR (95% CI)	Events	Person-years	IRR (95% CI)	Events	Person-years	IRR (95% CI)
Risk of cardiovascular events												
Baseline	2480	27,250	1.00 (reference)	4,209	32,891	1.00 (reference)	17	402	1.00 (reference)	4	34	1.00 (reference)
Pre-risk (-90 to 0 days)	367	815	4.51 (4.03 - 5.05)	19	1,101	0.13 (0.08-0.20)	3	9	4.42 (1.17-16.67)	0	1	N/A (---- ----)
Risk (1-30 days)	506	2,384	2.45 (2.21 - 2.71)	443	4,159	0.80 (0.72-0.89)	10	31	5.44 (2.10-14.10)	1	4	0.43 (0.01-15.82)
Risk (31-90 days)	324	2,357	1.50 (1.32 - 1.69)	456	4,128	0.77 (0.69-0.86)	7	31	3.73 (1.29-10.80)	0	4	N/A (---- ----)
Risk (90+ days)	467	3,386	1.43 (1.27 - 1.62)	1,231	8,537	1.07 (0.98-1.17)	8	85	1.10 (0.30-4.02)	1	12	12 (0.00-8.89)
Post-risk (1-30 days)	65	531	1.31 (1.02 - 1.68)	86	749	0.89 (0.72-1.11)	0	6	N/A (---- ----)	0	1	N/A (---- ----)
Risk of stroke												
Baseline	1,175	14,308	1.00 (reference)	2,042	16,312	1.00 (reference)	12	293	1.00 (reference)	4	31	1.00 (reference)
Pre-risk (-90 to 0 days)	212	434	5.49 (4.72 - 6.38)	6	547	0.09 (0.07-0.11)	2	7	4.29 (0.87 - 21.23)	0	1	N/A (---- ----)
Risk (1-30 days)	321	1,253	3.51 (3.07 - 4.01)	226	2,055	0.60 (0.57-0.63)	8	25	5.80 (1.91 - 17.61)	0	3	N/A (---- ----)
Risk (31-90 days)	196	1,239	2.06 (1.75 - 2.42)	267	2,040	0.68 (0.65-0.71)	6	24	4.25 (1.26 - 14.26)	0	3	N/A (---- ----)
Risk (90+ days)	284	1,779	2.07 (1.77 - 2.43)	636	4,310	1.38 (1.34-1.41)	6	69	1.01 (0.21 - 4.76)	1	10	0.51 (0.01 - 20.82)
Post-risk (1-30 days)	33	276	1.50 (1.06 - 2.14)	41	366	0.90 (0.82-0.99)	0	5	N/A (---- ----)	0	1	N/A (---- ----)
Risk of IHD												
Baseline	1,353	13,388	1.00 (reference)	2,158	16,533	1.00 (reference)	3	75	1.00 (reference)	0	2	1.00 (reference)
Pre-risk (-90 to 0 days)	155	393	3.51 (2.96 - 4.17)	13	551	0.17 (0.10 - 0.29)	1	2	13.34 (0.42 - 428.54)	0	0.2	N/A (---- ----)
Risk (1-30 days)	196	1,182	1.59 (1.35 - 1.86)	209	2,079	0.71 (0.61 - 0.82)	1	5	9.42 (0.34 - 258.63)	1	0.3	N/A (---- ----)
Risk (31-90 days)	125	1,169	0.95 (0.77 - 1.15)	196	2,063	0.62 (0.52 - 0.72)	1	5	9.42 (0.34 - 258.63)	0	0.3	N/A (---- ----)
Risk (90+ days)	196	1,675	0.95 (0.79 - 1.14)	576	4,151	0.94 (0.83 - 1.07)	1	14	N/A (---- ----)	0	0.3	N/A (---- ----)
Post-risk (1-30 days)	32	265	1.07 (0.75 - 1.53)	47	380	0.87 (0.65 - 1.17)	0	1	N/A (---- ----)	0	0.1	N/A (---- ----)
Risk of AMI												
Baseline	35	372	1.00 (reference)	122	990	1.00 (reference)	2	34	1.00 (reference)	0	2	1.00 (reference)
Pre-risk (-90 to 0 days)	8	12	6.42 (2.86 - 14.45)	0	34	N/A (---- ----)	0	0.2	N/A (---- ----)	0	0.2	N/A (---- ----)
Risk (1-30 days)	6	34	2.29 (0.91 - 5.78)	19	127	1.22 (0.71 - 2.10)	1	2	N/A (---- ----)	0	0.4	N/A (---- ----)
Risk (31-90 days)	1	33	0.39 (0.05 - 2.92)	13	127	0.88 (0.48 - 1.63)	0	2	N/A (---- ----)	0	0.4	N/A (---- ----)
Risk (90+ days)	6	42	1.05 (0.31 - 3.54)	43	278	1.37 (0.84 - 2.24)	1	2	N/A (---- ----)	0	0.9	N/A (---- ----)
Post-risk (1-30 days)	0	8	N/A (---- ----)	1	23	0.46 (0.06 - 3.31)	0	0.4	N/A (---- ----)	0	0.1	N/A (---- ----)

Abbreviations: National Health Insurance Database, NHID; Clinical Data Analysis and Reporting System, CDARS; The Health Improvement Network, THIN; ischemic heart disease, IHD; acute myocardial infarction, AMI; not available, N/A

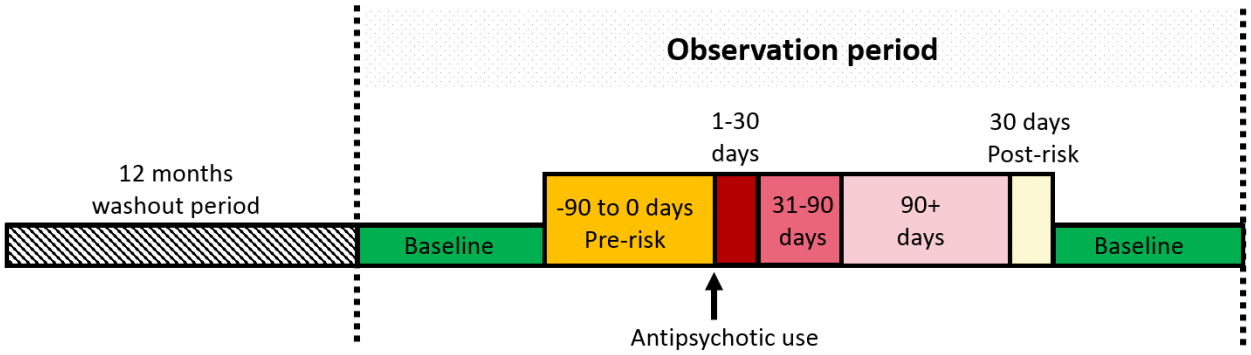
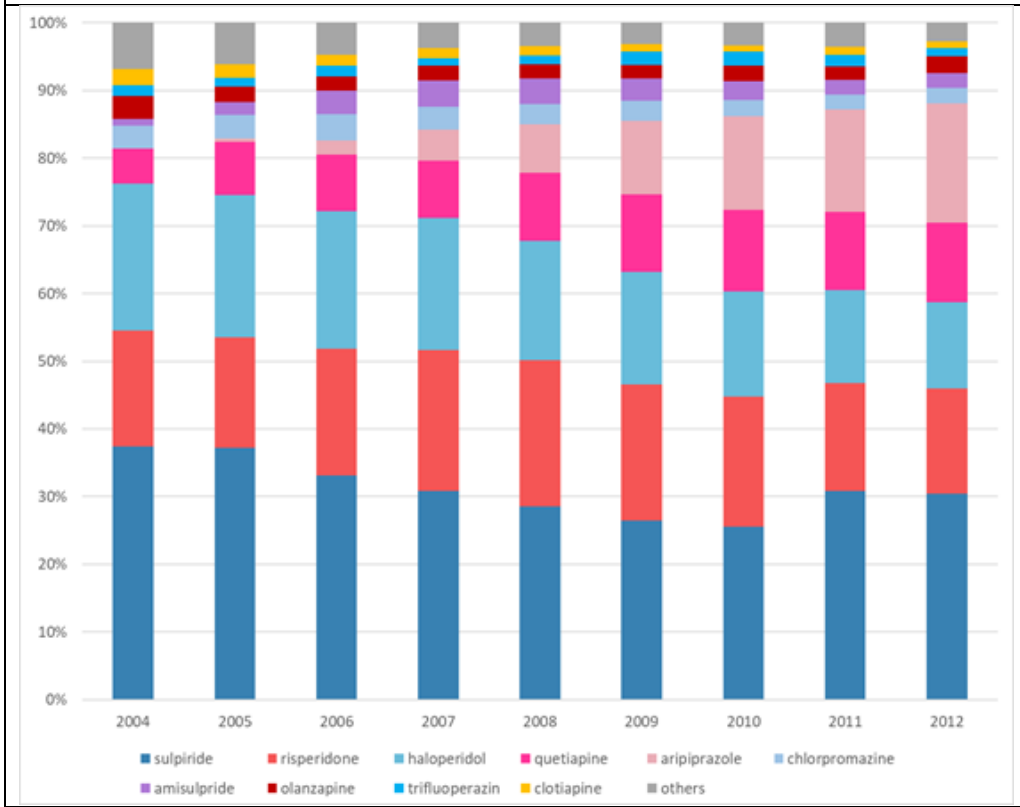


Figure 1. Schematic presentation of self-control case series

Taiwan



Korea

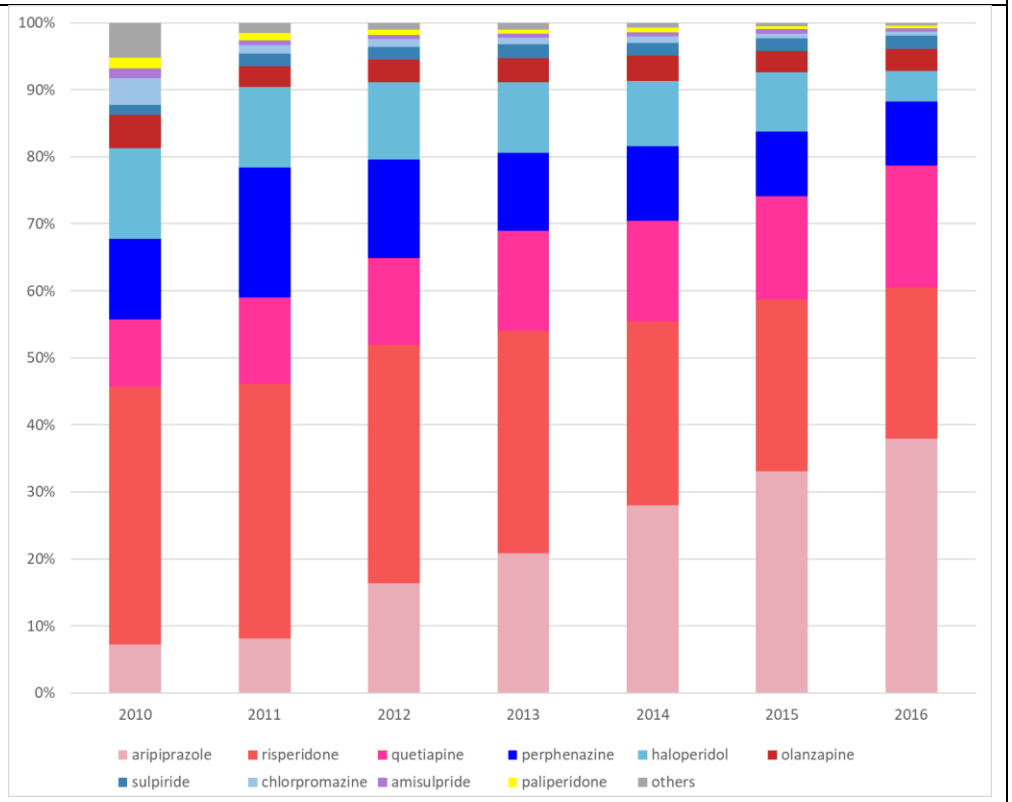
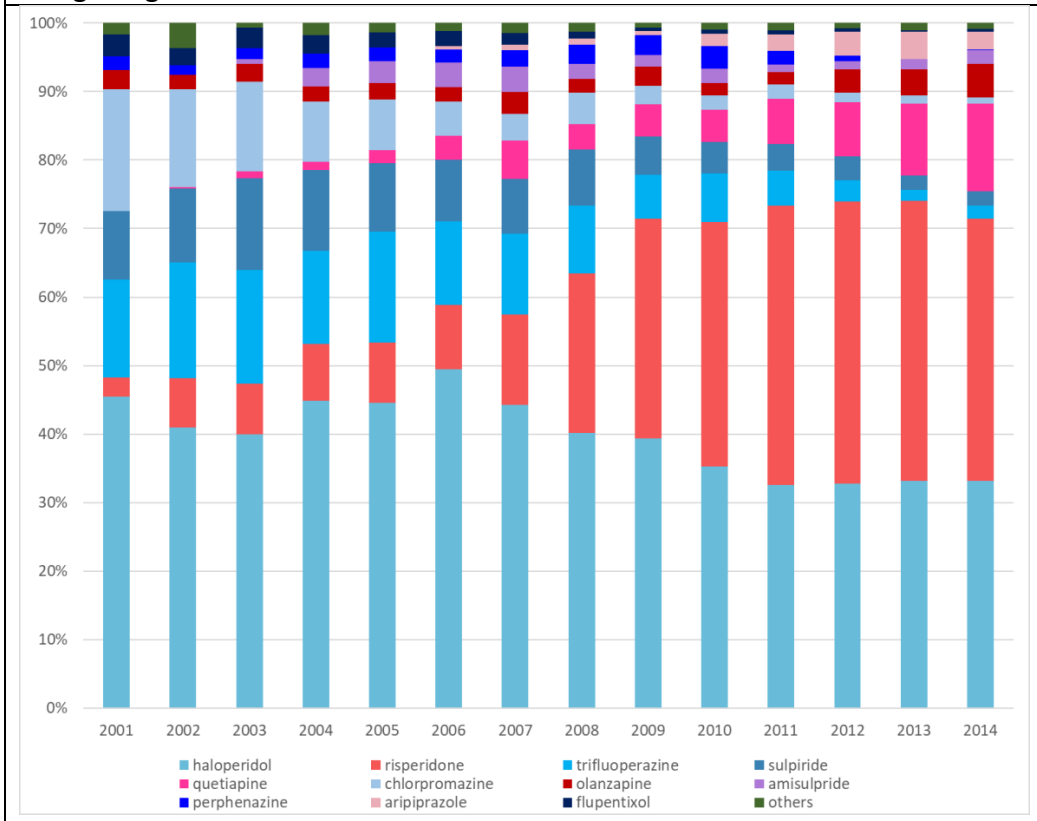


Figure 2. Utilization pattern of antipsychotics among countries

Hong Kong



UK

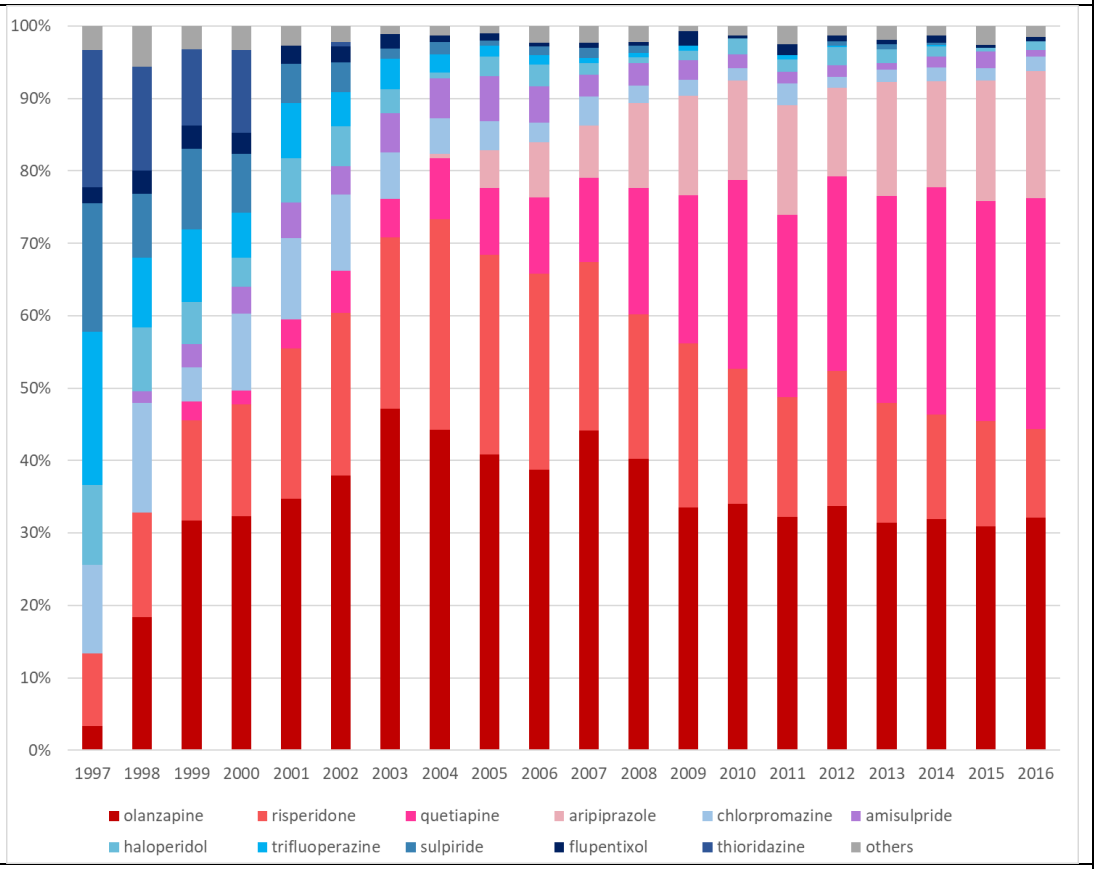


Figure 2. Utilization pattern of antipsychotics among countries (continued)

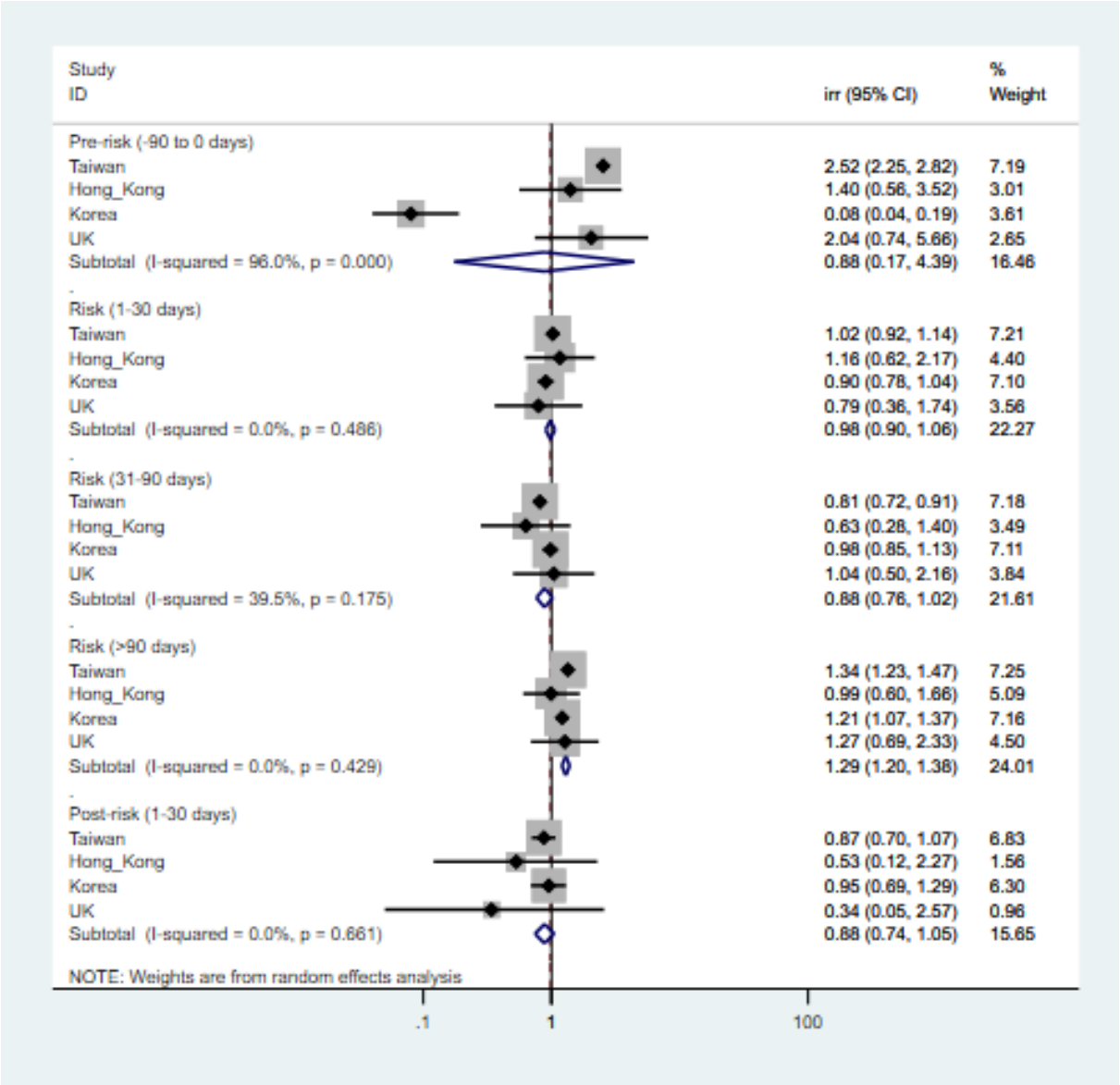


Figure 3. Pooled estimates of risk in metabolic events

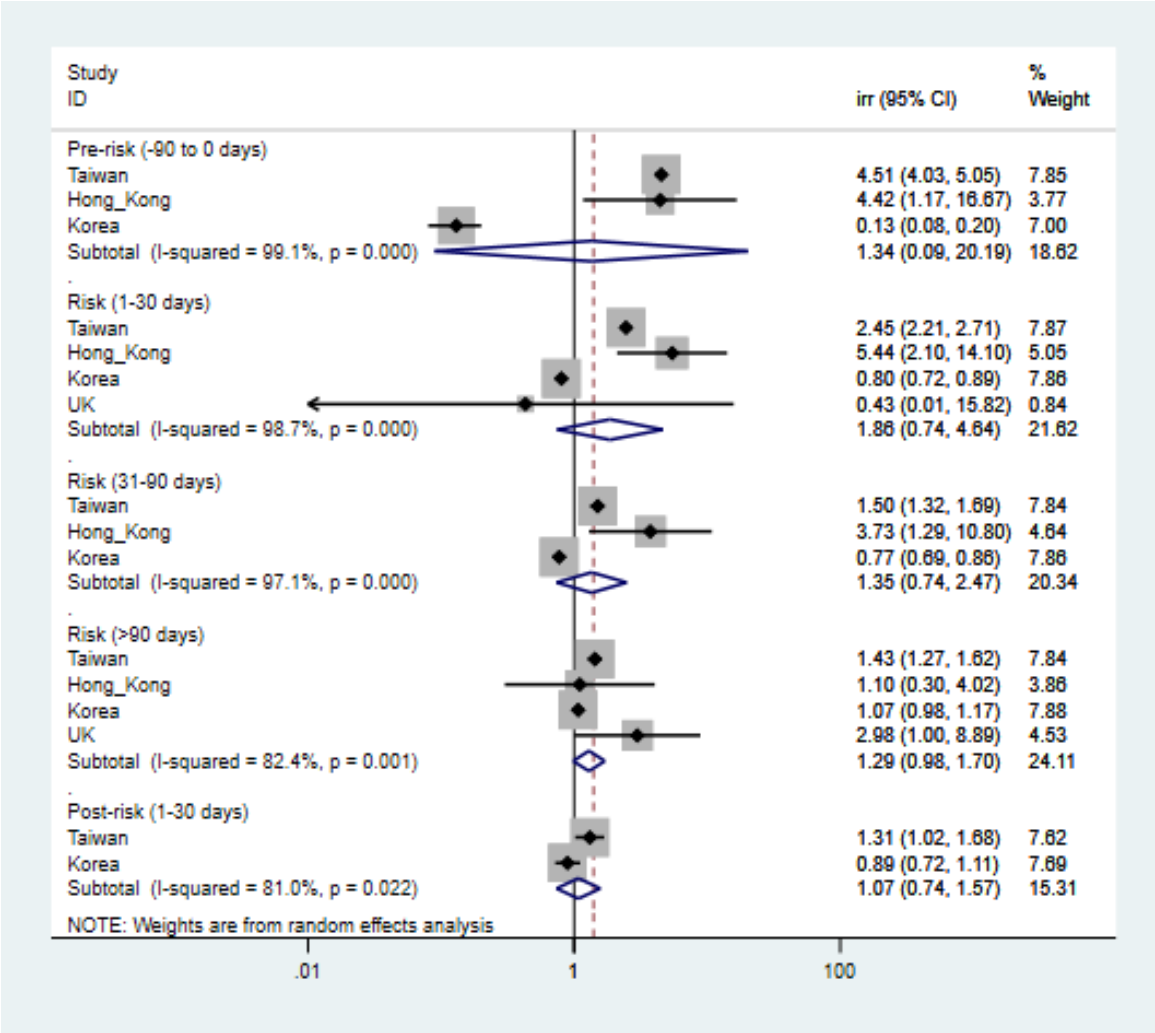


Figure 4. Pooled estimates for risk of cardiovascular events

Supplementary Table1. Participating Data Source

Taiwan's NHID (2003-2013)
The National Health Insurance Research Database (NHIRD) in Taiwan 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, health care professionals and facilities, service 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 unique, anonymous identifiers created by NHRI. All the antipsychotics and most prescription drugs are reimbursed by NHI in Taiwan, and all records of reimbursed drugs from inpatient, outpatient, emergency services and contracted pharmacy settings are included in NHIRD. Accuracy of the major disease diagnoses in the NHIRD, such as stroke, epilepsy, and acute coronary syndrome, has been validated.
South Korea Health Insurance Database (2010~2016)
The South Korean Health Insurance database has been widely used in the pharmaco-epidemiology field. Korea's national health insurance program was initiated in 1977 and achieved universal coverage of the entire population by 1989. The database contains all information on diagnoses and prescribed drugs for about 50 million Koreans. The database 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 Korean database includes all prescription information both in outpatient and inpatient settings, owing to a specific 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 70%.
Clinical Data Analysis and Reporting System of Hong Kong (2000~2014)
The Hong Kong Hospital Authority is a statutory body that manages all public hospitals and their outpatient clinics in Hong Kong. The Hospital Authority not only provides acute hospital care, but also provides acute and chronic disease management to patients in the community via outpatient clinics (both specialists and general physicians) throughout Hong Kong. Health services are available to all Hong Kong residents (over 7 million people). Data were extracted from the Clinical Data Analysis and Reporting System (CDARS), a database developed by the Hospital Authority. In 1995, the Hospital Authority developed the Clinical Management System (CMS), an electronic health record system that allows clinicians to order, document, and review care in their daily practice. 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.
The UK − THIN (1996~2016)
Two main large-scale databases in the UK are Clinical Practice Research Datalink (CPRD) and The Health Improvement Network (THIN). CPRD includes medical records data from 684 practices, representing approximately 15 million UK patients, and THIN contains records from 587 practices,

representing approximately 12 million UK patients. The THIN database was established in 2003 as a collaboration between In Practice Systems (INPS) who developed Vision software used by general practitioners (GPs) in the UK to manage patient data, and IMS Health who then provide access to the data for use in medical research. The UCL Research Departments Primary Care & Population Health (PCPH) and Infection & Public Health (IPH) have acquired a full license to THIN for the purposes of conducting large-scale epidemiological, clinical and health care utilization studies. The database contains records of 12 million patients, equivalent to 75.6 million patient years, covering 6.2% of the UK population. Patient files include sex, age and date of entering and leaving. Medical diagnoses are coded according to Read code and medications according to ATC code. All data are fully anonymous, processed and validated by CSD Medical Research UK.

Supplementary Table 2. Diagnosis code in the study

Variables	ICD-9	ICD-10
Mental disorder	290-319	F00-F99
Cancer	140-239	C00-D48
Congenital heart disease	745-747	Q20-Q24
Type 1 diabetes mellitus	250.X1, 250.X3 (X=0-9)	E10
Stroke	430-437	I60-69
Ischemic heart disease (IHD)	411, 413, 414	I20-25
Acute myocardial infarction (AMI)	410	I21
Hypertension	401-405	I10-15
Type 2 diabetes mellitus (DM)	250.X0, 250.X2 (X=0-9)	E11-14
Dyslipidemia	272	E78

Supplementary Table 3. Common data model

Demographic table

Id	Id_birthday	Sex (male=1, female=0, others=999)
10001	1972-09-08	1
10002	1990-12-28	0
10003	1993-11-05	999

Eligible table

Id	Enrol_in_date	Enrol_out_date
10001	1995-03-01	2013-12-31
10002	1995-03-01	2012-09-08
10003	2000-10-08	2013-05-06
10004	2005-07-20	2013-12-31

Medication table

Id	Atccode*	Rx_date	Rx_end	Supply_day	Setting (IP=inpatient; OP=outpatient)
10001	N05AH03	2013-08-01	2013-08-07	7	IP
10001	N05AH03	2013-09-01	2013-09-29	28	IP
10001	A10BA02	2014-10-12	2014-10-18	7	OP
10001	A10BA02	2015-10-05	2015-10-18	14	IP

Diagnostic table

Id	Icd9*	Event_date	Setting (IP=inpatient; OP=outpatient)
10001	4010	2013-09-01	IP
10002	41301	2014-10-08	IP
10003	431	2015-07-20	OP
10004	25002	2015-09-30	OP

*Icd9=ICD-9 (NHIRD), ICD-10 (CDARS), Read code (THIN)

Supplementary Table 4. ATC codes for antipsychotics

ATC code	Drug
First-generation antipsychotics	
N05AA01	Chlorpromazine
N05AA02	Levomepromazine
N05AA05	Triflupromazine
N05AB02	Fluphenazine
N05AB03	Perphenazine
N05AB06	Trifluoperazine
N05AC02	Thioridazine
N05AD01	Haloperidol
N05AD08	Droperidol
N05AF01	Flupentixol
N05AF02	Clopenthixol
N05AF03	Chlorprothixene
N05AF04	Tiotixene
N05AF05	Zuclopenthixol
N05AG02	Pimozide
N05AL01	Sulpiride
Second-generation antipsychotics	
ATC code	Drug
N05AE04	Ziprasidone
N05AE05	Lurasidone
N05AH01	Loxapine
N05AH02	Clozapine
N05AH03	Olanzapine
N05AH04	Quetiapine
N05AL05	Amisulpride
N05AX08	Risperidone
N05AX11	Zotepine
N05AX12	Aripiprazole
N05AX13	Paliperidone
N05AX14	Iloperidone