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Original Contribution

Metabolic Events Associated with Use of Antipsychotics in Children, Adolescents and Young Adults: A Multinational Sequence Symmetry Study

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ABSTRACT

It is known that younger patients treated with antipsychotics are at increased risk of metabolic events; however, it is unknown how this risk varies according to ethnicity, the class of antipsychotic and the specific product used, and by age group. We conducted a multinational sequence symmetry study in Asian populations (Hong Kong, Japan, Korea, Taiwan and Thailand) and non-Asian populations (Australia and Denmark) to evaluate metabolic events associated with antipsychotics in both Asian and non-Asian populations, for typical and atypical antipsychotics, and by the subgroups of children and adolescents, and young adults. Patients aged 6-30 years newly initiating oral antipsychotic drugs were included. We defined a composite outcome for metabolic events which included dyslipidemia, hypertension and hyperglycemia. We calculated the sequence ratio (SR) by dividing the number of people for whom a medicine for one of the outcome events was initiated within a 12-month period after antipsychotic initiation by the number before antipsychotic initiation. This study included 346,904 antipsychotic initiators across seven countries. Antipsychotic use was associated with an increased risk of composite metabolic events with a pooled adjusted SR (ASR) of 1.22 (95% CI 1.00-1.50). Pooled ASRs were similar between Asian (ASR, 1.22; 95% CI 0.88-1.70) and non-Asian populations (ASR, 1.22; 95% CI 1.04-1.43). The pooled ASR for typical and atypical antipsychotics were 0.98 (95% CI 0.85-1.12) and 1.24 (95% CI 0.97-1.59), respectively. No difference was observed in the relative effect in children and adolescents compared to young adults. The risk of metabolic events associated with antipsychotics use was similar in magnitude in Asian and non-Asian populations despite the marked difference in drug utilization patterns.

Keywords: antipsychotics, metabolic events, pediatrics, sequence symmetry analysis, multi-national data

INTRODUCTION

Over the past decades, there has been increased concern over the potential for premature death among youths treated with antipsychotics for behavioral and emotional problems [1-3]. It has been hypothesized that this increased risk of death may be partly driven by weight gain and other metabolic abnormalities, such as obesity, hyperglycemia and dyslipidemia, potentially induced by antipsychotics [1, 4]. As a result of these metabolic abnormalities, the use of antipsychotics can also lead to an increased risk of type 2 diabetes mellitus (T2DM) and other cardiovascular diseases (CVDs) [5]. Metabolic syndromes, such as hyperglycemia, obesity, dyslipidemia and hypertension, are associated with a 5-fold increased risk of T2DM and a 2-fold increased risk of developing CVD over the next 5-10 years [6].

The use of atypical antipsychotics has increased among adults and youth, internationally, since the early 1990s [7, 8]. Atypical antipsychotics have some of the most complex pharmacological properties in psychopharmacology [9]. Beyond antagonism of serotonin ($5HT_{2A}$) and dopamine (D_2) receptors, agents in this class interact with multiple other receptor subtypes for both dopamine and serotonin, and have effects on other neurotransmitter systems [10]. No two atypical antipsychotics have identical binding properties, which may explain why they possess distinct clinical properties [11]. For instance, among atypical antipsychotics, clozapine, olanzapine, quetiapine and risperidone have higher binding affinity with the H_1 histamine receptor and the $5HT_{2C}$ serotonin receptor [12]. As H_1 histamine receptors and $5HT_{2C}$ serotonin receptors are reported to be associated with increased risk of weight gain, especially when these receptors are blocked at the same time, this may lead to differences in side

effect profiles among antipsychotics [12].

Differences in genes encoding the $5HT_{2C}$ serotonin receptor, especially the rs1414334 C allele [13], have been observed between different ethnic populations; 10% of Americans and 15% of Europeans carry this allele, whereas only 1% of the Asian population carry it. Previous studies have suggested that increased risk of metabolic syndrome with the use of clozapine or risperidone is particularly pronounced in carriers of the rs1414334 C allele [13], leading to a potential difference in the risk of metabolic side effects in antipsychotics users with different ethnicities. Moreover, some pharmacogenetic polymorphisms have been reported that contribute to antipsychotic-induced metabolic syndrome, including leptin, ghrelin, tumor necrosis factor alpha, adiponectin, D_2 dopamine receptor, H_1 histamine-receptor, and alpha 1, beta 2 and beta 3 adrenergic receptor genes (Correll et al, 2004). For example, Thomas et al have reported that the D_2 TaqI polymorphism was associated with metabolic events in the Asian population. (Thomas GN 2002). Furthermore, metabolizer status of CYP2D6 may influence metabolism and plasma concentrations of antipsychotics. As the genotype distribution differs considerably between ethnicities, this might lead to variations in risk of metabolic events: there are 1% to 2% ultra-rapid metabolizers and 5% to 10% poor metabolizers in European populations, whereas only 1% to 2% poor metabolizers in Asian populations [14].

We hypothesized that the risk of metabolic events posed by the use of antipsychotics will vary according to ethnicity, the class of antipsychotics, and the specific product used. We hypothesized that olanzapine, quetiapine and risperidone would have a greater risk of metabolic syndrome than other atypical antipsychotics due to the binding affinity

with the H_1 histamine receptor and the $5HT_{2C}$ serotonin receptor. We also hypothesized that the risk would be lower in countries with more people of Asian ethnicity because the increased risk of metabolic syndrome with the use of risperidone is particularly pronounced in carriers of the rs1414334 C allele, which is present in 10% of Americans and 15% of Europeans, but only in 1% of the Asian population. We therefore conducted a multi-national study to evaluate metabolic events associated with antipsychotics in both Asian and non-Asian populations, for typical and atypical antipsychotics, specific product used and subgroups of children and adolescents, and young adults.

METHODS

Common Protocol and Distributed Network Approach

We used a common protocol to study the risk of metabolic events associated with use of antipsychotics in individuals aged 6 to 30 years of age in seven countries across Asia (Hong Kong, Japan, Korea, Taiwan and Thailand), Oceania (Australia) and Europe (Denmark). All data sources were generated from automated capture of patient-level electronic data from either administrative clinical records or administrative claims records in a defined population or portion thereof. Additional details about the included databases and study years can be found in the Appendix Table 1 and the reports by Lai et al. (2015), Mellish (2015) et al. and Ilomäki et al. (2020). In brief, we included four claims databases, 2 electronic health records databases, and one registry database with a total of about 40 million individuals. This study has been approved by Human Research Ethics Committees or Data Custodian External Requests Committees on the basis of each site's regulations.

A distributed network model was established, requiring participating sites to create a common minimum dataset containing (a) a unique patient identifier, (b) a variable to identify the medicine dispensed based on the World Health Organization (WHO) standard Anatomical Therapeutic Chemical (ATC) code, and (c) a variable to identify the date of medicine supply. The statistical analysis code was developed as a stand-alone SAS program for execution by each participant in their home institution. This approach eliminates the complex programming burden for participants and overcomes barriers due to language and disparate data structures. Standardised summary results were returned to the coordinating centre in Taiwan for collation.

Sequence Symmetry Analysis (SSA)

We included patients aged 6-30 years who were new users of an oral antipsychotic drug. New users were defined as those who had not been dispensed the medicine of interest in the previous one year. We conducted a sequence symmetry analysis (SSA) [15] which is a method for detecting signals of potential adverse drug events by utilizing computerized health data [16]. Validation studies have indicated that SSA has moderate sensitivity, high specificity and robust performance [17, 18]. SSA is based on analyzing the sequences of medications; if the outcome medication is more often initiated after antipsychotics than before, it may be an indication of an adverse effect of antipsychotics [15].

We calculated the sequence ratio (SR) by dividing the number of people for whom the outcome medication was initiated after antipsychotics (index medication) by the number of people for whom the outcome medication was initiated before antipsychotics within a 12-month period. As such, the SR can be regarded as an estimate of the ratio

of incidence rate of the outcome in the exposed period versus the non-exposed period [15, 18]. The SSA may be affected by prescribing trends over time which may possibly lead to a biased effect estimate. To adjust for this time trend, we calculated a null-effect SR derived by the calculation of the probability of each incident index drug user being exposed to an outcome drug within the specified exposure window after the day the antipsychotic (index medication) was initiated [19]. The adjusted SR (ASR) was then calculated as the crude SR divided by the null-effect SR. The corresponding 95% confidence interval was derived from bootstrapping with 10,000 samples of the ASR [20].

Index and Outcome Medications

We used the Anatomical Therapeutic Chemical (ATC) Classification System to capture the records of medicines [21]. We included new use of any of the antipsychotics listed in **Appendix Table 2** as index medications. These antipsychotics were selected because they are commonly used for the younger population in each participating country. We considered a composite metabolic event as our primary outcome, including medicines dispensed to treat dyslipidemia, hypertension and hyperglycemia. The medications included were antihypertensive drugs (ATC codes: C03A, C03C, C09, C07, C08CA) for hypertension, oral blood glucose-lowering drugs (ATC code: A10B) for hyperglycemia, and lipid-modifying agents (ATC code: C10) for dyslipidemia. We excluded propranolol (ATC codes: C07AA05) from the list of antihypertensive drugs because it may be used for the control of anxiety or tremor but only rarely for hypertension. We used antihypertensive, antidiabetic or lipid-modifying drugs as outcome indicators for metabolic events since the use of these drugs in a young population can be assumed to reflect that the metabolic event was overt and required

treatment.

Statistical Analysis

The primary analysis assessed the risk of composite metabolic events associated with the use of any antipsychotics. Further subgroup analyses were conducted based on stratification by different population groups (Asian vs non-Asian), different outcomes (hypertension, hyperglycemia and dyslipidemia), age groups (children and adolescents aged 6-18 and young adults aged 19-30), medication classes (typical vs atypical antipsychotics, and individual medicines: haloperidol, olanzapine, risperidone, quetiapine and sulpiride, the five most commonly used antipsychotics. The ASRs from each site were pooled using DerSimonian and Laird's random-effect model with the corresponding 95% confidence interval [22]. I^2 statistic and Cochran's Q-test were used to test for heterogeneity and subgroup difference, respectively, with a p-value <0.1 indicating statistical significance [23]. Datasets from two sites, Thailand and Japan, may not be representative of the whole population, as the data from Thailand only came from 3 hospitals whereas data from Japan only included claims from people in the work force and their dependents. We therefore conducted a sensitivity analysis by removing Thailand and Japan from the analysis to estimate this impact. All analyses were conducted by SAS version 9.4 and RevMan version 5.2.

RESULTS

In total, we identified 346,904 antipsychotic initiators aged between 6 and 30 years across seven countries (3,871 in Korea, 93,291 in Japan, 266 in Hong Kong, 11,050 in Australia, 43,532 in Denmark, 193,534 in Taiwan and 1,360 in Thailand), of whom

53.3% were male. The detailed age distribution is shown in **Appendix Figure 1**. Notably, 19.7% of antipsychotics users in Thailand were aged 6 or below, compared to 6.1% in Taiwan, 3.0% in Australia, 2.6% in Japan and less than 1% for the other countries. Differences in the antipsychotic agent initiated across countries were observed. The most common antipsychotic was aripiprazole in Japan, quetiapine in Australia and risperidone in Denmark, Hong Kong, Korea, Taiwan and Thailand. (**Appendix Figure 2**)

Antipsychotic initiation was associated with an increased risk of composite metabolic events with a pooled ASR of 1.22 (95% CI 1.00-1.50). We observed a high heterogeneity (I^2=78%) of the ASRs between sites with ASRs ranging from 0.37 in Thailand to 6.4 in Hong Kong. The effect was similar in Asian (ASR=1.22; 95% CI 0.88-1.70) and non-Asian (ASR=1.22; 95% CI 1.04-1.43) populations (test with subgroup difference p=0.99) (**Figure 1**). Regarding the individual outcomes, an association was found for dyslipidemia only (pooled ASR=1.51; 95% CI: 1.18-1.93) with moderate heterogeneity (I^2=50%) in ASRs; the ASR in each site varied from 0.27 (Thailand) to 1.95 (Hong Kong) with statistically significant results in Japan, Taiwan and Denmark only (**Figure 2a to 2c**).

In the analysis stratified by age groups, the pooled ASR was 1.23 (95% CI 0.95-1.60) in children and adolescents (**Figure 3a**) and 1.25 (95% CI 1.08-1.43) in young adults (**Figure 3b**), however there was no statistically significant difference between the age groups (test for subgroup difference: p=0.95). The pooled ASR in typical antipsychotics for composite metabolic events was 0.98 (95% CI 0.85-1.12) and the pooled ASR in atypical antipsychotics was 1.24 (95% CI 0.97-1.59) (**Figure 4a and 4b**). The subgroup

difference was marginally non-significant between typical and atypical antipsychotics with I^2=63% (test for subgroup difference: p=0.1). None of the ASR for the individual agents except for risperidone (ASR=1.18; 95% CI 1.00-1.39) reached statistical significance. (**Figure 4c to 4g**). Sensitivity analyses excluding Thailand and Japan yielded similar results (**Appendix Figure 3 and 4**). The results of subgroup analysis for specific outcomes by typical and atypical antipsychotics respectively are presented in **Appendix Table 3**. The numbers of patients in each country used for SSA of outcomes (about composite metabolic events, specific outcomes, and subgroup analysis) are presented in Appendix Table 4.

DISCUSSION

This study investigated the risk of metabolic events associated with new use of antipsychotics among children, adolescents and young adults across 7 countries. We found that antipsychotic initiation was associated with a 22% increased risk of a composite measure of metabolic events, whereby although dyslipidemia, hypertension and hyperglycemia are often correlated, the magnitude of the risk for individual events varied. Our results suggest that the effect of antipsychotics was similar across age groups and different ethnicities. However, there is some suggestion that the risk may vary according to class of antipsychotic used.

Despite the pharmacological differences in metabolizing enzymes between these populations suggested in the literature, the risk of metabolic events was not different between the Asian and non-Asian populations overall (22% increase in both Asian and non-Asian populations) nor for the individual outcomes, that is hypertension (15%

increase in Asian-, 22% increase in non-Asian populations), hyperglycemia (7% increase in Asian-, 23% increase in non-Asian populations), and dyslipidemia (53% increase in Asian-, 46% increase in non-Asian populations). As such, our results suggest that the differences in genetic composition, at the population level, may not have a major impact on metabolic effects related to the use of antipsychotics. However, we observed a high heterogeneity of effect estimates across the Asian populations, with I^2=78% for the composite metabolic event outcome. Considering the relatively similar genetic composition among Asians, this may further support that genetic effect may not have a huge impact on this association and any differences in risk identified could potentially be due to differences in the healthcare systems, the database settings, and lifestyle factors of the included countries [25].

Heterogeneity observed among Asian populations could also be due to variability in the antipsychotic prescribing patterns across countries. Asian countries varied more in the antipsychotic drugs used, while in Denmark and Australia similar patterns were observed in the distribution of antipsychotic drug types. In view of potentially fatal adverse effects such as agranulocytosis, clozapine should not be prescribed as an incident antipsychotic treatment [26]. In some participating sites (e.g. Hong Kong), genetic testing is required before prescribing drugs with a high risk of agranulocytosis, which may account for the difference in the utilization pattern observed. We found that there was a marked difference in the use of sulpiride among the participating sites, with Taiwan having the most patients initiated with this medication while sulpiride was rarely, if ever used in Denmark and not used at all in Australia. Although previous studies supported the effectiveness of sulpiride in adults [27], little is known about its safety in children and adolescents. We did not find an association between sulpiride and

metabolic events. Further, in our subgroup analyses focusing on individual antipsychotics, we found that risperidone was associated with an increased risk of metabolic events; olanzapine tended to pose a higher risk of metabolic events although with no statistical significance; and no association between quetiapine and risk of metabolic events was observed except in Denmark. While many of the results were not statistically significant, the point estimates were about 10-15% higher risk in Denmark and Australia compared to Asian countries. Polymorphisms might be one of the likely explanations for the observed association between quetiapine and risk of metabolic events in Denmark but not in other countries [28]. We found the ASR of haloperidol was less than one, reflecting that more patients initiated their metabolic treatment before receiving their first prescription for haloperidol. The result showed there was no increased risk for patients after the initiation of haloperidol, rather than that haloperidol led to a decreased risk of metabolic events. One might hypothesize that some clinicians prefer using haloperidol in patients with a history of metabolic disorders, but the hypothesis requires additional analysis for confirmation.

Atypical antipsychotics are widely dispensed by child- and adolescent psychiatrists for the treatment of various disorders, and there is growing evidence that children who take antipsychotic drugs are at a higher risk of weight gain and metabolic syndrome than adolescents and adults [29-31]. Many of the current clinical guidelines suggest the use of atypical antipsychotics, in particular aripiprazole and quetiapine, for children and adolescents who require antipsychotic treatment [2, 32-34]. Our results indicate that aripiprazole and quetiapine were increasingly used as the first antipsychotic treatment in most of the sites, and thus further studies focusing on the long-term effect of these medications are required in both children and adults. We found that olanzapine was

commonly used in most countries but not Thailand, as olanzapine was indicated for prevention of chemotherapy-induced nausea and vomiting but not for psychiatric disorders. Consistent with previous studies [2, 4, 35], we found that olanzapine may pose a higher risk of metabolic events in some countries (Australia and Denmark). Previous studies have suggested that the use of olanzapine has decreased over time in most countries [36, 37]. However, we could only identify this trend in Denmark and South Korea. In view of the popularity of olanzapine, clinicians should be aware of possible metabolic events and be cautious when initiating olanzapine for those with existing high risk.

We found antipsychotics were associated with an increased risk of metabolic events in young adults. Although there was no statistical significance, the risk point estimate of children and adolescents was similar to the young adult group, highlighting potential risk of metabolic events. Importantly, our results showed that metabolic events were occurring in the first year of treatment, and were likely to be of clinical significance as medication was required. Given the young age of our cohort and increasing use of antipsychotics for off-label indications, our results highlight the need for metabolic monitoring in all children and young adults who are treated with antipsychotics. Healthcare providers should be cautious when using these treatments for off-label indications in children, adolescents and young adults or those with milder forms of disease.

The main strength of this study is the large data sets available for analysis across multiple countries. Also, we used a common protocol method and distributed analytic approach which ensured results were comparable regarding the statistical analytical

program and data variables used [38-40]. Our study investigated the association between antipsychotics and metabolic events using SSA, which has the advantage of inherently addressing measured and unmeasured confounders that are stable over time [15] as many of the metabolic factors such as baseline blood pressure or lipid profiles are not commonly recorded in databases [41]. However, this study has limitations. First, the dataset used in some of the participating sites may not be representative of the entire population (Thailand, Japan). However, risk estimates did not show a material difference after removing the above mentioned sites from our analyses. Second, our study may not have enough power in some of the stratified analyses. Third, concomitant use of multiple antipsychotics was not considered, although the rate of such concomitant use can be assumed to be very low in children, adolescents and young adults. Fourth, as with all studies using claims databases, we were not able to confirm whether metabolic abnormalities really occurred by using laboratory examination results. Although we used the records of antihypertensive, antidiabetic or lipid-modifying drugs as indicators for metabolic events, we may have failed to identify cases with mild conditions not requiring medical treatment. Fifth, we performed a standard SSA including any users who ever received antipsychotics for intention-to-treat analysis, examining the propensity of chronological order of incident prescriptions of the index drug before versus after the outcome drug (Hallas 1996). Therefore bias toward null is possible if the antipsychotic was used to treat a short-term condition. Moreover, we did not consider dose-response relationship for metabolic risk in the SSA because the dosage and some clinical information (e.g., body mass index) is not available for some countries. Our results should be interpreted with caution because the observed risk differences may possibly be explained by different treatment guidelines and protocols of the included countries. Finally, we cannot exclude the possibility that

some of the differences observed across countries may be due to differences in health-care practice as we observed a major difference in the choice of antipsychotics in different countries.

CONCLUSION

We provide further evidence of the association between use of antipsychotics and the risk of metabolic events. We have identified that the risk is of similar magnitude in children and adolescents and in young adults. There is some suggestion that the risk may vary according to class of antipsychotics used. While the risk of metabolic events was significantly increased, the effect was similar between populations despite the marked difference in drug utilization patterns and genetic composition between Asian and non-Asian countries and amongst the Asian countries.

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CONFLICT OF INTEREST

All authors declare no potential confict of interest.

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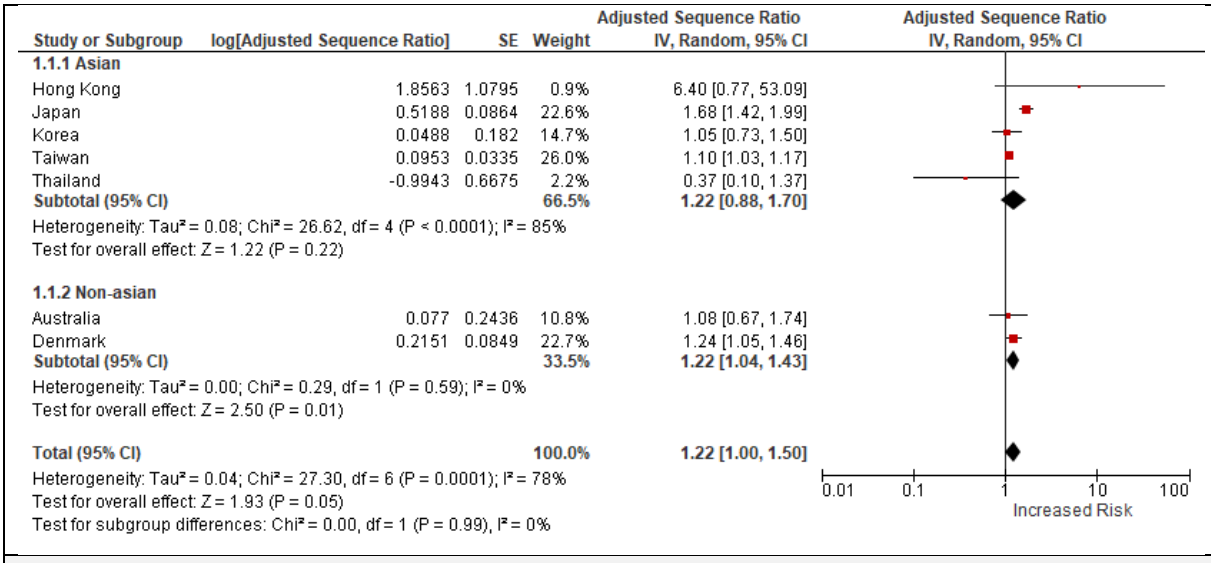
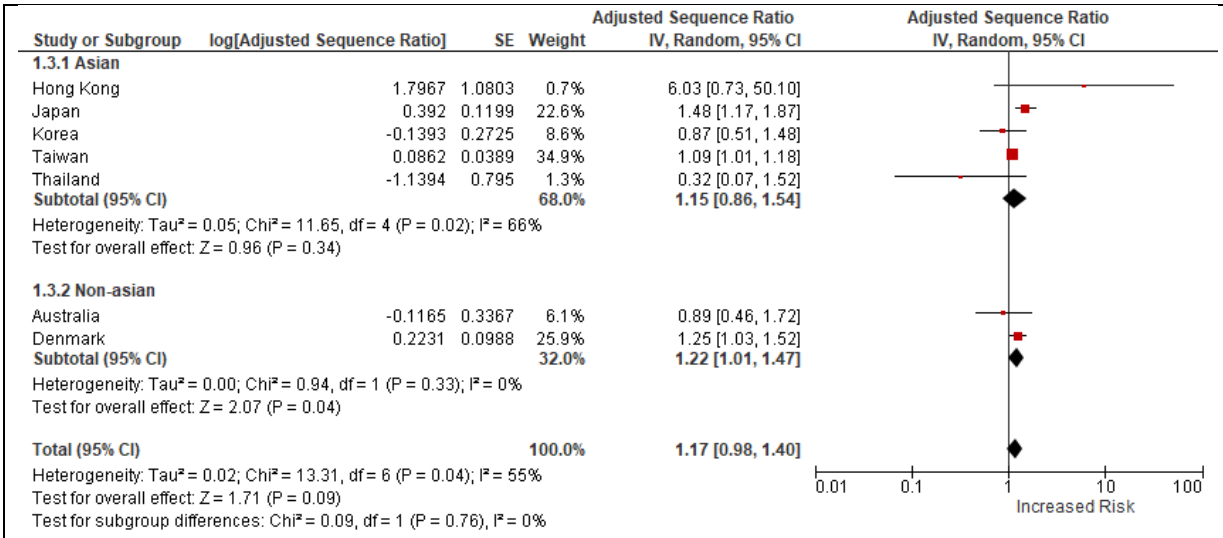
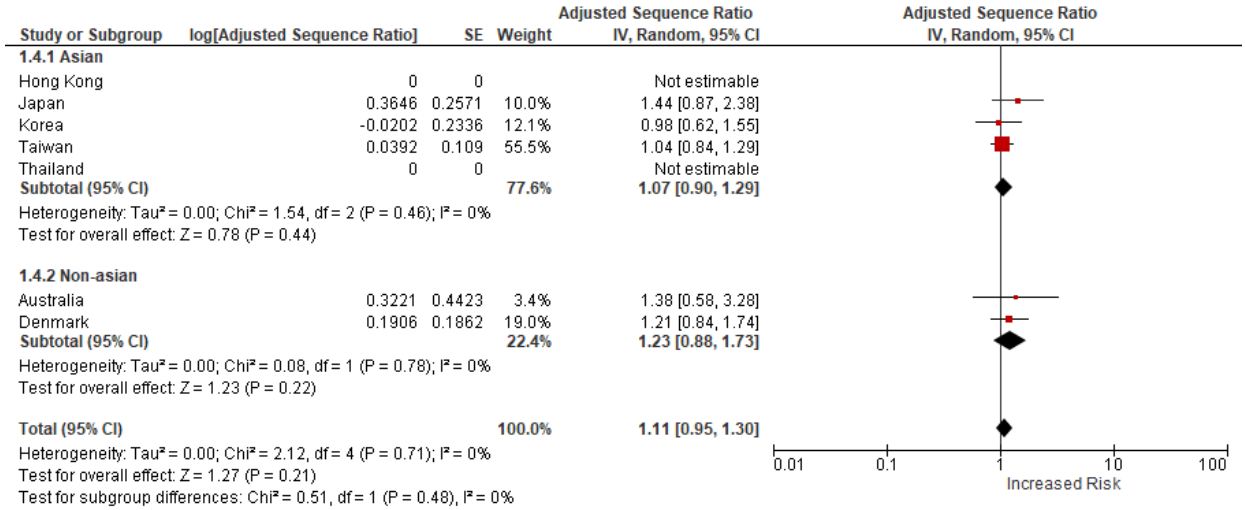


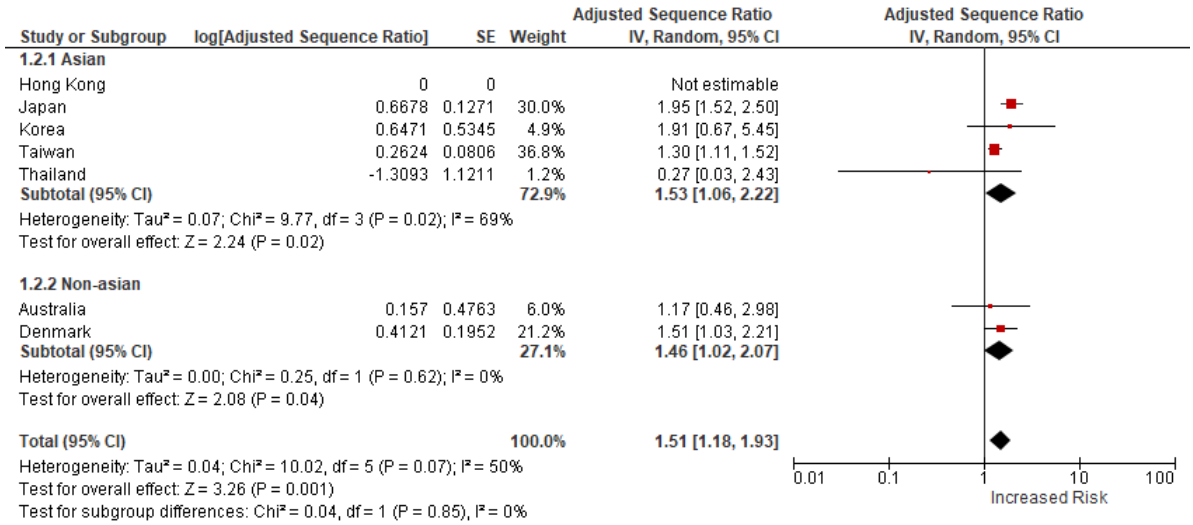
Figure 1: Associations between ***antipsychotics*** and ***composite metabolic events***



(2a) *Hypertension*

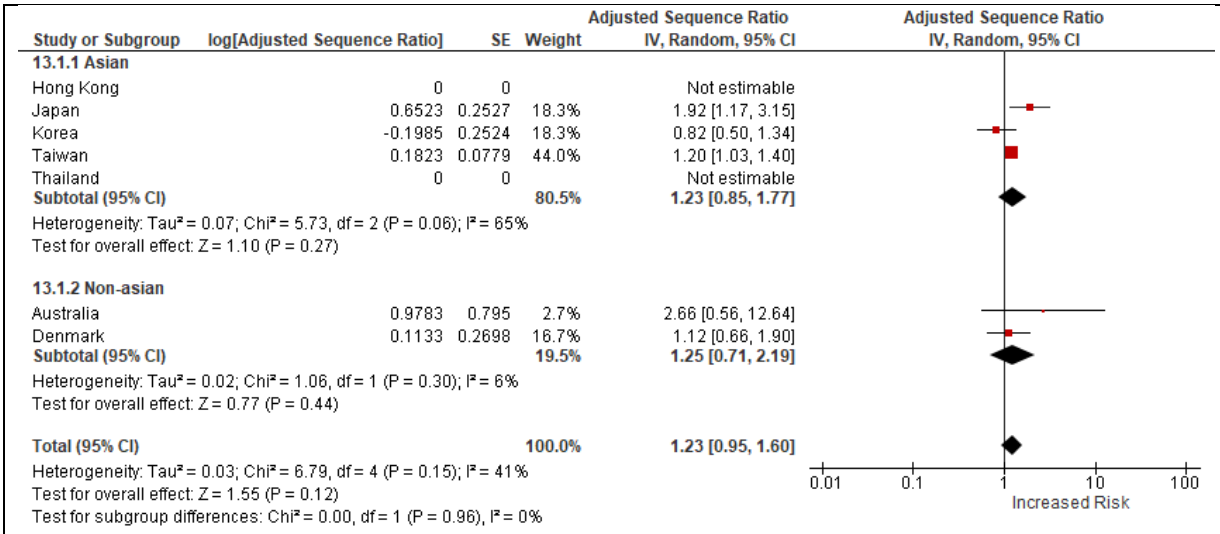


(2b) *Hyperglycemia*

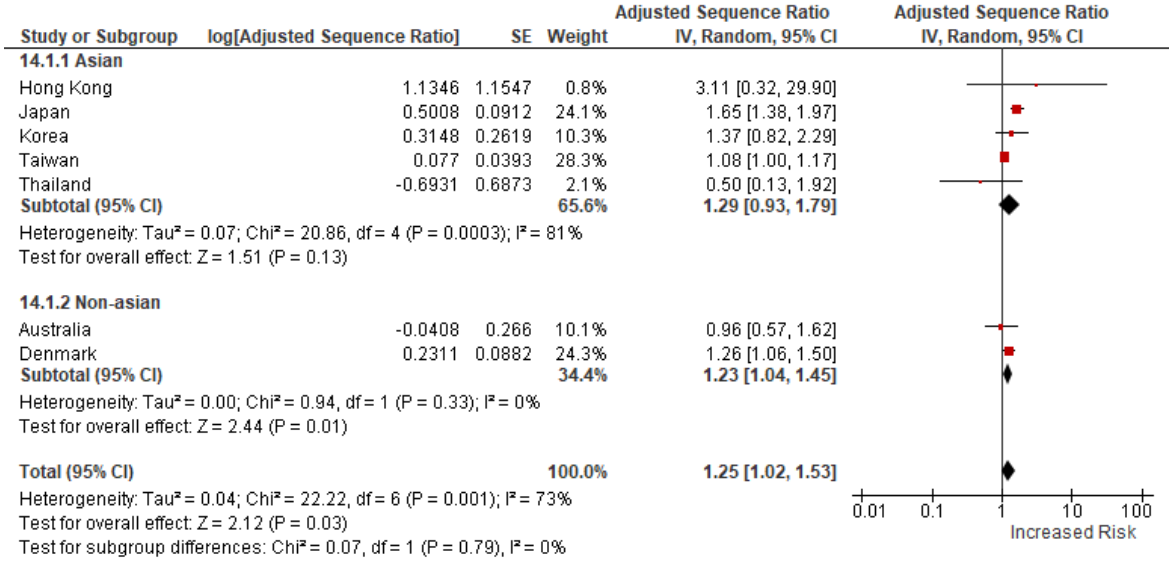


(2c) *Dyslipidemia*

Figure 2. Associations between ***antipsychotics*** and ***specific outcomes*** (2a: Hypertension; 2b: Hyperglycemia; 2c: Dyslipidemia)

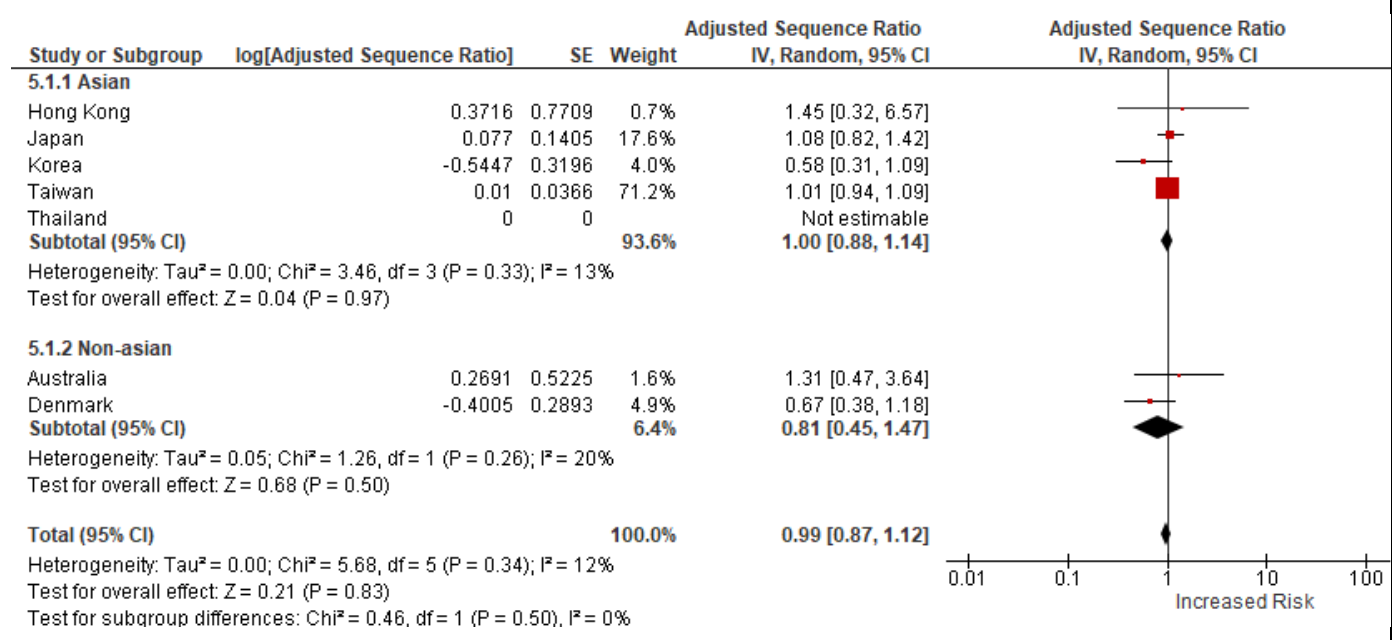


(3a) ***Children and Adolescents***

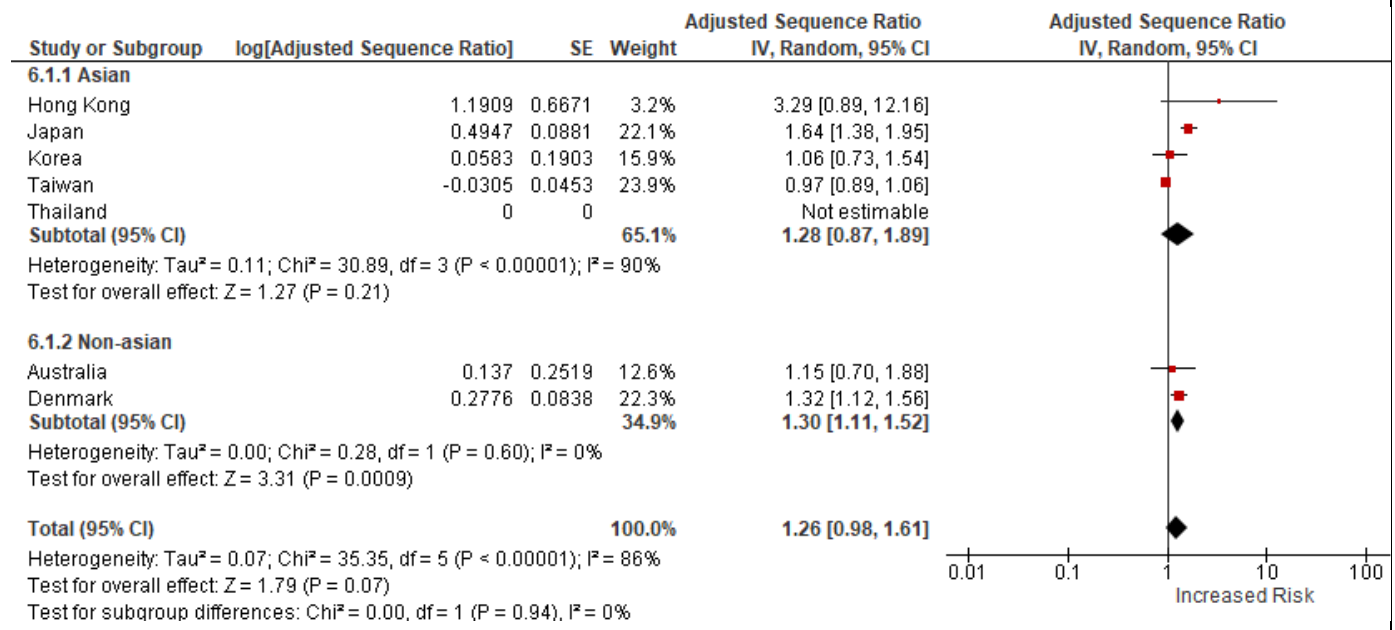


(3b) ***Young Adults***

Figure 3. Associations between ***antipsychotics*** and ***composite metabolic event*** in the subgroup of (3a) Children and Adolescents and (3b) Young Adults

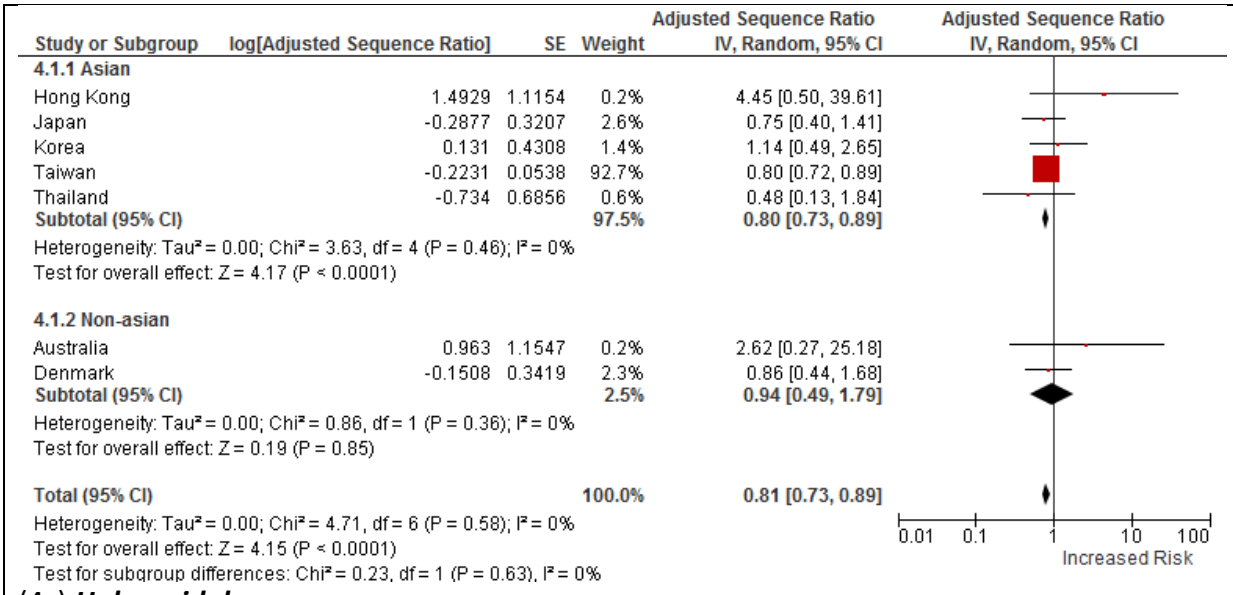


(4a) ***Typical Antipsychotics***

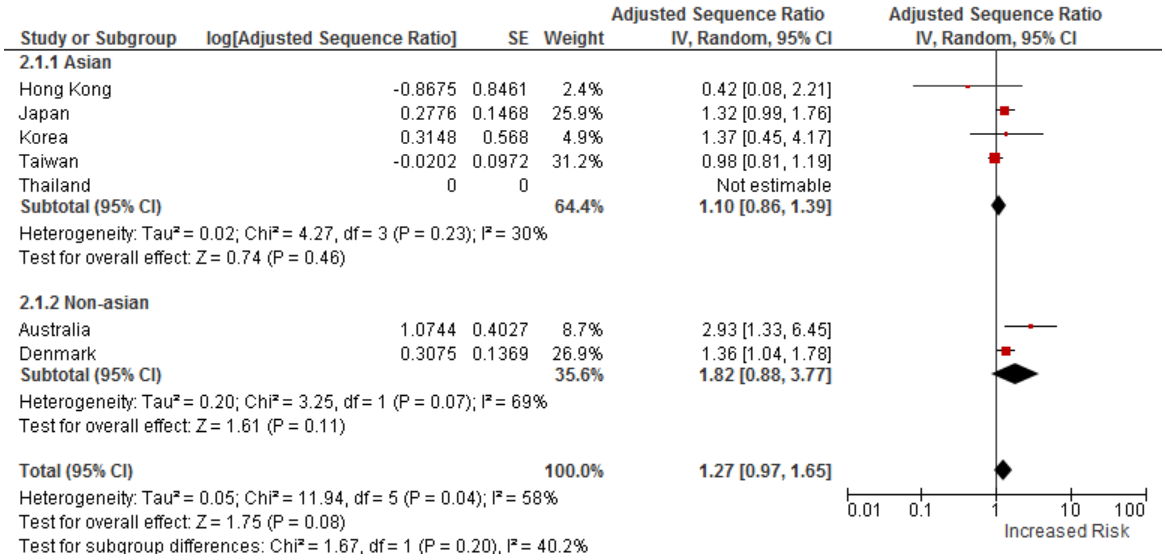


(4b) ***Atypical Antipsychotics***

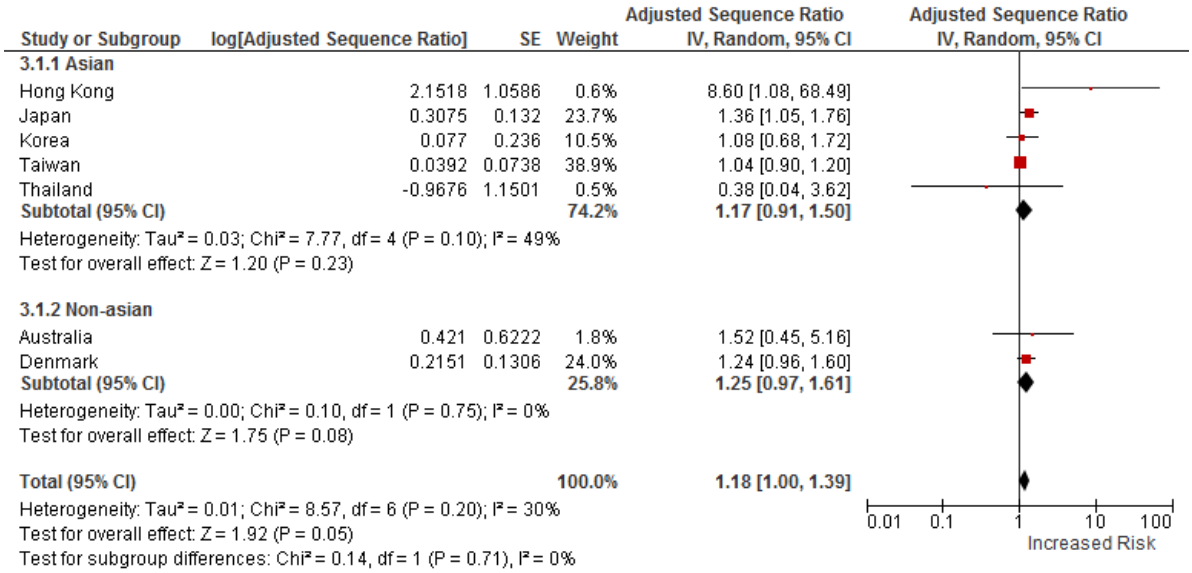
Figure 4. Subgroup analysis: associations between ***different antipsychotics*** and ***composite metabolic event***. (4a) Typical Antipsychotics, (4b) Atypical Antipsychotics, (4c) Haloperidol, (4d) Olanzapine, (4e) Risperidone, , (4f) Quetiapine or (4g) Sulpride



(4c) ***Haloperidol***

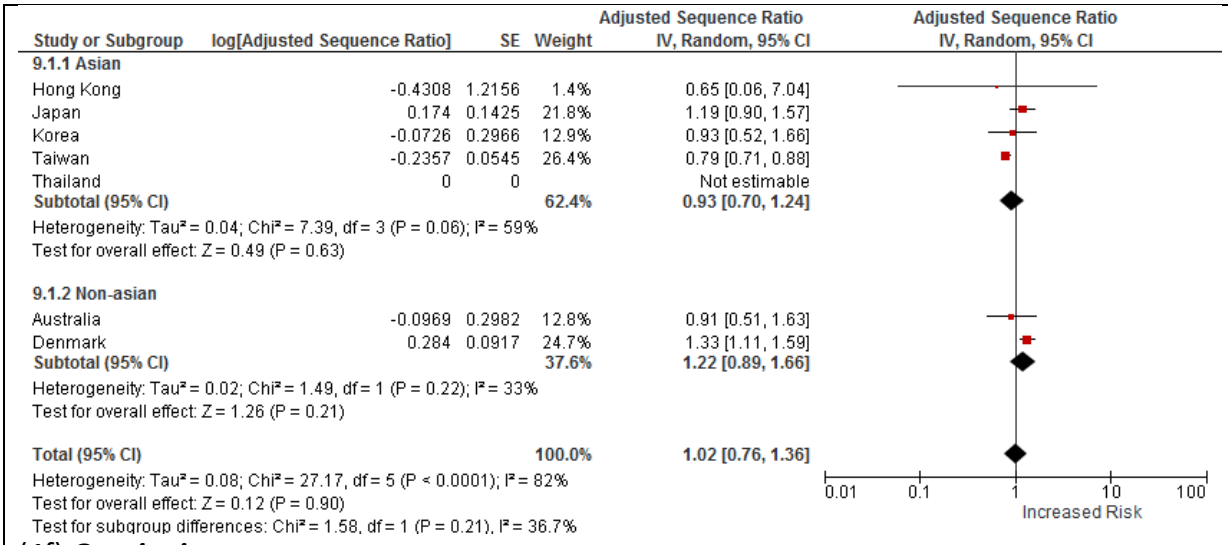


(4d) ***Olanzapine***

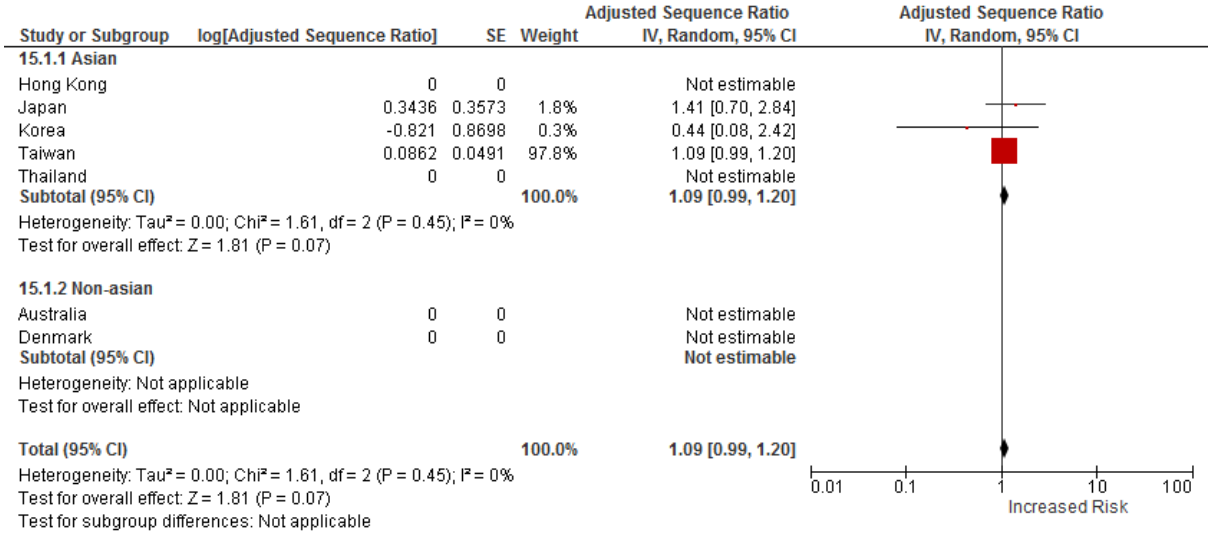


(4e) ***Risperidone***

Figure 4. (continued)



(4f) ***Quetiapine***



(4g) ***Sulpiride***

Figure 4. (continued)

Appendix Table 1. Summary of Participating Databases

Country	Database name (abbreviation)	Source type	Starting year for the study	Ending year for the study	Estimated No. of individuals in the database	Percentage covered of the total population?
Hong Kong	Clinical Data Analysis and Reporting System (CDARS)	National EHR	2008	2013	700,000	1% random sample
Japan	Japan Medical Data Center Database (JMDC)	Claims database	2009	2016	> 2.3 million	2%[a]
Korea	Korean National Health Insurance Database	Claims database	2002	2013	> 50 million	~100%
Taiwan	National Health Insurance Database (NHID)	Claims database	2003	2013	> 25 million	~100%
Thailand	Thai Electronic Hospital Databases	Hospital EHR	2005	2016	300,000 individuals.	0.4%[b]
Australia	Australian Pharmaceutical Benefits Scheme	Claims database	2013	2016	2.4 million	10% random sample
Denmark	Danish Nationwide Health Registries	Registry	2000	2016	> 5 million	~100%

[a] enrollees of work force and their dependents

[B]Patients from three academic hospitals

Appendix Table 2. Codes for antipsychotics

ATC code	Index antipsychotics	
Typical		
	Chlorpromazine	N05AA01
	Fluoperazine	N05AB06
	Haloperidol	N05AD01
	Pimozide	N05AG02
	Sulpiride	N05AL01
	Thioridazine	N05AC02
Atypical		
	Amisulpride	N05AL05
	Aripiprazole	N05AX12
	Clozapine	N05AH02
	Olanzapine	N05AH03
	Paliperidone	N05AX13
	Quetiapine	N05AH04
	Risperidone	N05AX08
	Ziprasidone	N05AE04

Appendix Table 3. Subgroup analysis: associations for specific outcomes by typical and atypical antipsychotics

	Typical antipsychotics				atypical antipsychotics			
	Causal group	Non-causal group	Adjusted Sequence Ratio	95% CI	Causal group	Non-causal group	Adjusted Sequence Ratio	95% CI
Dyslipidemia								
Asian								
Hong Kong	NA	NA	NA	NA	NA	NA	NA	NA
Japan	NA	NA	NA	NA	26	20	1.15	(0.64 - 2.05)
Korea	NA	NA	NA	NA	NA	NA	NA	NA
Taiwan	411	406	0.97	(0.84 - 1.11)	244	263	0.89	(0.74 - 1.05)
Thailand	NA	NA	NA	NA	NA	NA	NA	NA
Non-Asian								
Australia	NA	NA	NA	NA	NA	NA	NA	NA
Denmark	NA	NA	NA	NA	25	18	1.23	(0.67 - 2.25)
Hyperglycemia								
Asian								
Hong Kong	NA	NA	NA	NA	NA	NA	NA	NA
Japan	11	19	0.51	(0.24 - 1.08)	39	20	1.73	(1.01 - 2.97)
Korea	9	11	0.57	(0.24 - 1.38)	39	29	1.00	(0.62 - 1.61)
Taiwan	166	150	1.08	(0.87 - 1.35)	103	98	1.04	(0.79 - 1.37)
Thailand	NA	NA	NA	NA	NA	NA	NA	NA
Non-Asian								
Australia	NA	NA	NA	NA	NA	NA	NA	NA
Denmark	NA	NA	NA	NA	NA	50	1.27	(0.89 - 1.83)
Hypertension								
Asian								
Hong Kong	NA	NA	NA	NA	NA	NA	NA	NA
Japan	55	59	0.90	(0.62 - 1.30)	161	107	1.46	(1.14 - 1.86)
Korea	8	15	0.48	(0.20 - 1.14)	24	23	0.94	(0.53 - 1.66)
Taiwan	1120	1258	0.94	(0.87 - 1.02)	696	829	0.89	(0.80 - 0.98)
Thailand	NA	NA	NA	NA	NA	NA	NA	NA
Non-Asian								
Australia	NA	NA	NA	NA	NA	NA	NA	NA
Denmark	20	24	0.76	(0.42 - 1.37)	239	170	1.31	(1.08 - 1.60)

NA= not available because the number is considered an identifiable number

Appendix Table 4. The number of patients of each country used for SSA for outcomes

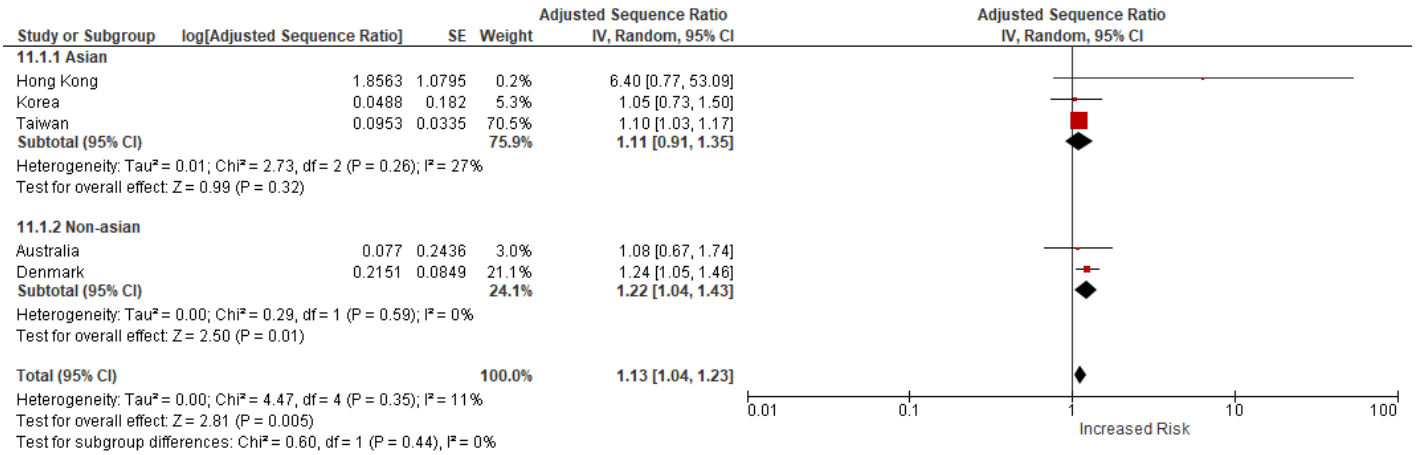
Country	Age groups	# of causal/ # of non-causal group	Crude SR
Risk Evaluations: antipsychotics - metabolic syndrome (composite)			
Taiwan	Overall	1867 / 1807	1.03
	Young Adult	1505 / 1483	1.01
	Child & Adolescent	362 / 324	1.12
Korea	Overall	71 / 54	1.31
	Young Adult	40 / 23	1.74
	Child & Adolescent	31 / 31	1.00
Japan	Overall	376 / 215	1.75
	Young Adult	324 / 192	1.69
	Child & Adolescent	52 / 23	2.26
Hong Kong	Overall	NA / NA	NA
	Young Adult	NA / NA	NA
	Child & Adolescent	NA / NA	NA
Thailand	Overall	NA / NA	NA
	Young Adult	NA / NA	NA
	Child & Adolescent	NA / NA	NA
Denmark	Overall	339 / 252	1.35
	Young Adult	307 / 227	1.35
	Child & Adolescent	32 / 25	1.28
Australia	Overall	37 / 30	1.23
	Young Adult	29 / 28	1.04
	Child & Adolescent	NA / NA	4.00
Risk Evaluations: olanzapine - metabolic syndrome (composite)			
Taiwan	Overall	451 / 236	0.91
	Young Adult	395 / 209	0.89
	Child & Adolescent	56 / 27	2.07
Korea	Overall	NA / NA	NA
	Young Adult	NA / NA	NA
	Child & Adolescent	NA / NA	NA
Japan	Overall	185 / 78	1.37
	Young Adult	159 / 67	1.37
	Child & Adolescent	26 / 11	1.36
Hong Kong	Overall	NA / NA	NA
	Young Adult	NA / NA	NA
	Child & Adolescent	NA / NA	NA
Thailand	Overall	NA / NA	NA
	Young Adult	NA / NA	NA
	Child & Adolescent	NA / NA	NA
Denmark	Overall	234 / 94	1.49
	Young Adult	211 / 86	1.45
	Child & Adolescent	NA / NA	NA
Australia	Overall	NA / NA	NA
	Young Adult	NA / NA	NA
	Child & Adolescent	NA / NA	NA
Risk Evaluations: haloperidol - metabolic syndrome			
Taiwan	Overall	567 / 757	0.75
	Young Adult	491 / 658	0.75
	Child & Adolescent	76 / 99	0.77
Korea	Overall	NA / NA	NA
	Young Adult	NA / NA	NA
	Child & Adolescent	NA / NA	NA
Japan	Overall	18 / 23	0.78
	Young Adult	16 / 19	0.84

	Child & Adolescent	NA	/	NA	NA
Hong Kong	Overall	NA	/	NA	NA
	Young Adult	NA	/	NA	NA
	Child & Adolescent	NA	/	NA	NA
Thailand	Overall	NA	/	NA	NA
	Young Adult	NA	/	NA	NA
	Child & Adolescent	NA	/	NA	NA
Denmark	Overall	17	/	18	0.94
	Young Adult	13	/	16	0.81
	Child & Adolescent	NA	/	NA	NA
Australia	Overall	NA	/	NA	NA
	Young Adult	NA	/	NA	NA
	Child & Adolescent	NA	/	NA	NA
Risk Evaluations: risperidone- metabolic syndrome (composite)					
Taiwan	Overall	410	/	423	0.97
	Young Adult	314	/	321	0.98
	Child & Adolescent	96	/	102	0.94
Korea	Overall	42	/	31	1.35
	Young Adult	NA	/	NA	NA
	Child & Adolescent	22	/	22	1.00
Japan	Overall	140	/	99	1.41
	Young Adult	111	/	87	1.28
	Child & Adolescent	29	/	12	2.42
Hong Kong	Overall	NA	/	NA	NA
	Young Adult	NA	/	NA	NA
	Child & Adolescent	NA	/	NA	NA
Thailand	Overall	NA	/	NA	NA
	Young Adult	NA	/	NA	NA
	Child & Adolescent	NA	/	NA	NA
Denmark	Overall	145	/	106	1.37
	Young Adult	122	/	94	1.30
	Child & Adolescent	23	/	12	1.92
Australia	Overall	NA	/	NA	NA
	Young Adult	NA	/	NA	NA
	Child & Adolescent	NA	/	NA	NA
Risk Evaluations: Atypical antipsychotics- metabolic syndrome (composite)					
Taiwan	Overall	993	/	1098	0.90
	Young Adult	821	/	907	0.91
	Child & Adolescent	168	/	183	0.92
Korea	Overall	64	/	49	1.31
	Young Adult	37	/	20	1.85
	Child & Adolescent	27	/	29	0.93
Japan	Overall	342	/	201	1.70
	Young Adult	293	/	178	1.65
	Child & Adolescent	49	/	23	2.13
Hong Kong	Overall	NA	/	NA	NA
	Young Adult	NA	/	NA	NA
	Child & Adolescent	NA	/	NA	NA
Thailand	Overall	NA	/	NA	NA
	Young Adult	NA	/	NA	NA
	Child & Adolescent	NA	/	NA	NA
Denmark	Overall	348	/	245	1.42
	Young Adult	313	/	227	1.38
	Child & Adolescent	35	/	18	1.94
Australia	Overall	NA	/	NA	NA
	Young Adult	NA	/	NA	NA
	Child & Adolescent	NA	/	NA	NA

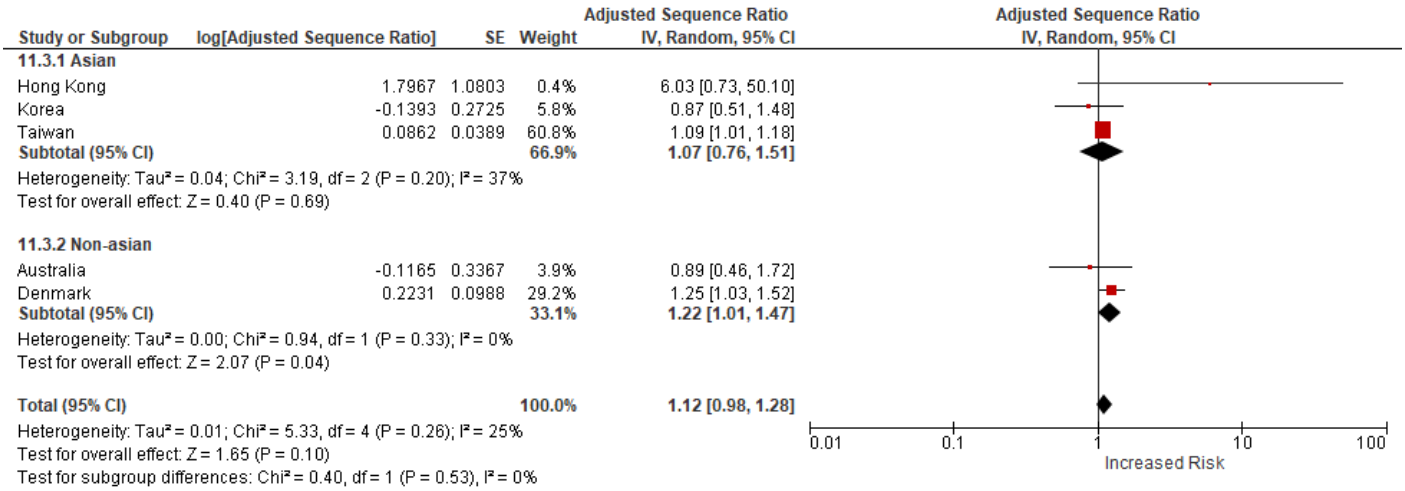
Risk Evaluations: Typical antipsychotics- metabolic syndrome (composite)					
Taiwan	Overall	1644	/	1743	0.94
	Young Adult	1382	/	1477	0.94
	Child & Adolescent	233	/	236	0.99
Korea	Overall	17	/	23	0.74
	Young Adult	11	/	14	0.79
	Child & Adolescent	NA	/	NA	NA
Japan	Overall	107	/	95	1.13
	Young Adult	98	/	87	1.13
	Child & Adolescent	NA	/	NA	NA
Hong Kong	Overall	NA	/	NA	NA
	Young Adult	NA	/	NA	NA
	Child & Adolescent	NA	/	NA	NA
Thailand	Overall	NA	/	NA	NA
	Young Adult	NA	/	NA	NA
	Child & Adolescent	NA	/	NA	NA
Denmark	Overall	21		28	0.75
	Young Adult	16	/	22	0.73
	Child & Adolescent	NA	/	NA	NA
Australia	Overall	NA	/	NA	NA
	Young Adult	NA	/	NA	NA
	Child & Adolescent	NA	/	NA	NA
Risk Evaluations: antipsychotics – dyslipidemia medications					
Taiwan	Overall	340	/	261	1.30
Korea	Overall	NA	/	NA	NA
Japan	Overall	194	/	96	2.02
Hong Kong	Overall	NA	/	NA	NA
Thailand	Overall	NA	/	NA	NA
Denmark	Overall	72	/	42	1.71
Australia	Overall	NA	/	NA	NA
Risk Evaluations: antipsychotics – hypertension medications					
Taiwan	Overall	1298	/	1260	1.03
Korea	Overall	27	/	28	0.96
Japan	Overall	183	/	120	1.53
Hong Kong	Overall	NA	/	NA	NA
Thailand	Overall	NA	/	NA	NA
Denmark	Overall	233	/	173	1.35
Australia	Overall	18	/	18	1.00
Risk Evaluations: antipsychotics – hyperglycemia medications					
Taiwan	Overall	176	/	164	1.07
Korea	Overall	42	/	31	1.35
Japan	Overall	39	/	24	1.63
Hong Kong	Overall	NA	/	NA	NA
Thailand	Overall	NA	/	NA	NA
Denmark	Overall	68	/	50	1.36
Australia	Overall	NA	/	NA	NA
NA= not available because the number is considered an identifiable number					

Appendix Figure 1. Age and sex distribution of the patients receiving antipsychotics among countries

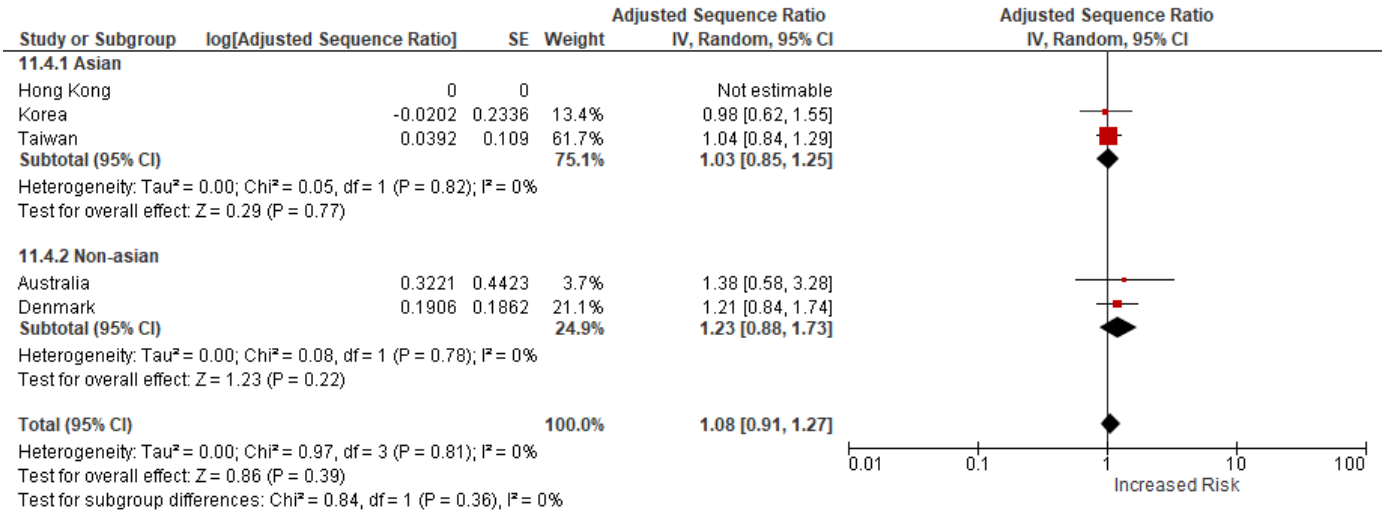
Appendix Figure 2. Distribution of antipsychotics use by year among countries



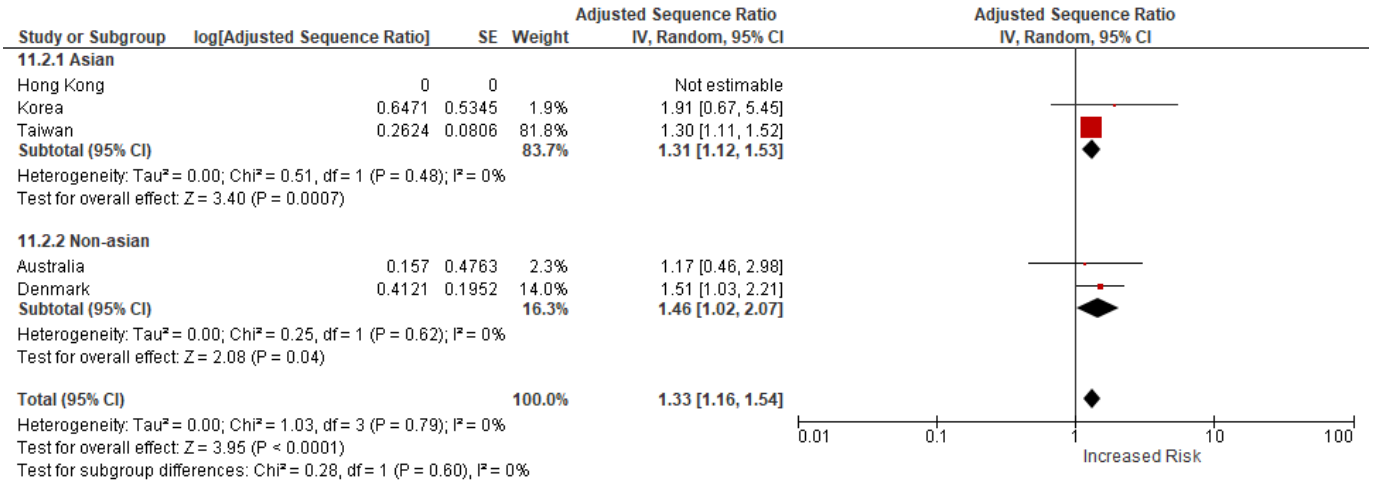
Appendix Figure 3. Sensitivity analysis: Associations between antipsychotics and composite metabolic events (excluding Thailand and Japan)



4a *Hypertension*



4b *Hyperglycemia*



c *Dyslipidemia*

Appendix Figure 4. Sensitivity analysis: associations between antipsychotics and individual outcomes (excluding Thailand and Japan). **(4a) Hypertension, (4b) Hyperglycemia, or (4c) Dyslipidemia.**

1. Cooper, S.J., et al., *BAP guidelines on the management of weight gain, metabolic disturbances and cardiovascular risk associated with psychosis and antipsychotic drug treatment.* J Psychopharmacol, 2016. **30**(8): p. 717-48.
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