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Associations among antipsychotics, metabolism-related diseases, and cataracts in patients with schizophrenia: A retrospective cohort study

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ABSTRACT

Background: Long-term cataract risks associated with first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs), and their associations with metabolism-related diseases are not yet elucidated.

Methods: Using Taiwan National Health Insurance data, we conducted a propensity score matched population-based cohort study consisting of 10,014 patients with newly diagnosed schizophrenia from 2005 to 2009 and followed them until the end of 2013. A Cox hazard model with metabolism-related diseases as time-dependent covariates was adapted to estimate the hazard ratio (HR) of cataracts between SGAs and FGAs groups.

Results: During the 8-year follow-up, patients receiving SGAs were associated with a higher risk of cataract than those receiving FGAs with an adjusted HR of 1.59 (95% confidence interval [CI] = 1.06 −2.36). Patients receiving high-metabolic-risk SGAs (clozapine and olanzapine) showed the highest risk of cataracts among SGAs when compared with those receiving FGAs (aHR = 2.57, 95% CI: 1.35−4.88). SGAs demonstrated a stronger contribution in the risk of cataract in patients without diabetes mellitus (DM) and hyperlipidemia than in those developed these diseases. Patients who developed DM or hyperlipidemia after receiving antipsychotics had an approximately 2.5-fold increased cataract risk over those who did not develop these diseases.

Conclusions: Regardless of the condition of metabolic-related diseases, SGAs were independently associated with an increased risk of cataract. DM and hyperlipidemia developed after antipsychotics contributed to the risk of cataract risk.

1. Introduction

Cataracts are the most common eye disease and a major cause of visual impairment and blindness worldwide (Pascolini and Mariotti, 2012). Risk factors for cataract development include aging, smoking, excessive sunlight exposure, steroid use, and diabetes mellitus (DM) (Robman and Taylor, 2005). People with psychotic disorders, especially schizophrenia, have a higher cataract risk than the general population (Viertio et al., 2007). Since the mid-1960s, an association has been indicated between the development of cataracts or retinopathy in patients with schizophrenia and the use of first-generation antipsychotics (FGAs) (Kim et al., 2010; Moura Filho et al., 2008; Razeghinejad et al., 2008) or second-generation antipsychotics (SGAs) (Borovik et al., 2009; Valibhai et al., 2001). FGAs and SGAs have different profiles and action mechanisms. In recent years, SGAs have been widely used because they are efficacious against schizophrenia symptoms and have fewer extrapyramidal effects (Tandon et al., 2008). However, little is known about the difference between FGAs and SGAs in terms of cataract risks. To date, only one study (Souza et al., 2008) has investigated this difference and showed that after adjusting for confounding factors, patients receiving FGAs had a higher cataract risk than those receiving SGAs. Because this study had a cross-sectional setting and small sample size, further studies are required to confirm the findings and evaluate long-term cataract risks between FGA and SGA groups.

Studies have indicated that antipsychotics increase the risk of metabolism-related diseases such as DM, hyperlipidemia,

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hypertension, and cardiovascular diseases (CVD) (Liao et al., 2011; Wang et al., 2015). The US Food and Drug Administration has indicated that SGAs have a therapeutic class effect as they are associated with increased risk of metabolic adverse effects (FDA, Feb, 2017 [Accessed 9 July 2017]). Although metabolism-related diseases such as DM and hyperlipidemia are known risk factors for cataract development (Lindblad et al., 2008; TsuTsUMI et al., 1999), associations among metabolism-related diseases, antipsychotics, and cataract risks in patients with schizophrenia are not yet elucidated.

This study aimed to evaluate long-term cataract risks for patients with schizophrenia between those receiving FGAs and SGAs by using nationwide registration data. We also assessed the effects of metabolism-related diseases on the association between antipsychotic drug use and cataract risks.

2. Methods

2.1. Data source

A population-based cohort study was conducted using the Registry for Catastrophic Illness Patient Database (RCIPD) linked to the Taiwan National Health Insurance Research Database (NHIRD). The RCIPD was established to track patients with major or catastrophic illnesses, including schizophrenia. The diagnosis and applications for patients with schizophrenia into the RCIPD are validated by psychiatrists' certification. The RCIPD included all relevant information about the "catastrophic illness certificate" status, such as diagnosis, date of diagnosis, and date of death. The NHIRD is derived from Taiwan's single-payer compulsory NHI program, which covers up to 99% of the 23 million people in Taiwan (www.nhi.gov.tw/english/index.aspx). The NHIRD documents all medical claims data on disease diagnoses, procedures, drug prescriptions, demographics, and enrollment profiles of all NHI beneficiaries (Wen et al., 2008). The database used in this study covered the period from January 1, 2005 and December 31, 2013.

2.2. Study design and population

We assembled a study cohort consisting of patients with newly diagnosed schizophrenia (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code: 295) in the RCIPD between January 1, 2005 and December 31, 2009. These patients were followed-up until the switch to the other antipsychotic group or discontinue, cataract occurrence, death, or end of the study (December 31, 2013), whichever came first.

Fig. 1 presents the flowchart of the study design and the process of patient selection. We included patients with incident schizophrenia aged 15 to 65 years old and received monotherapy of FGAs

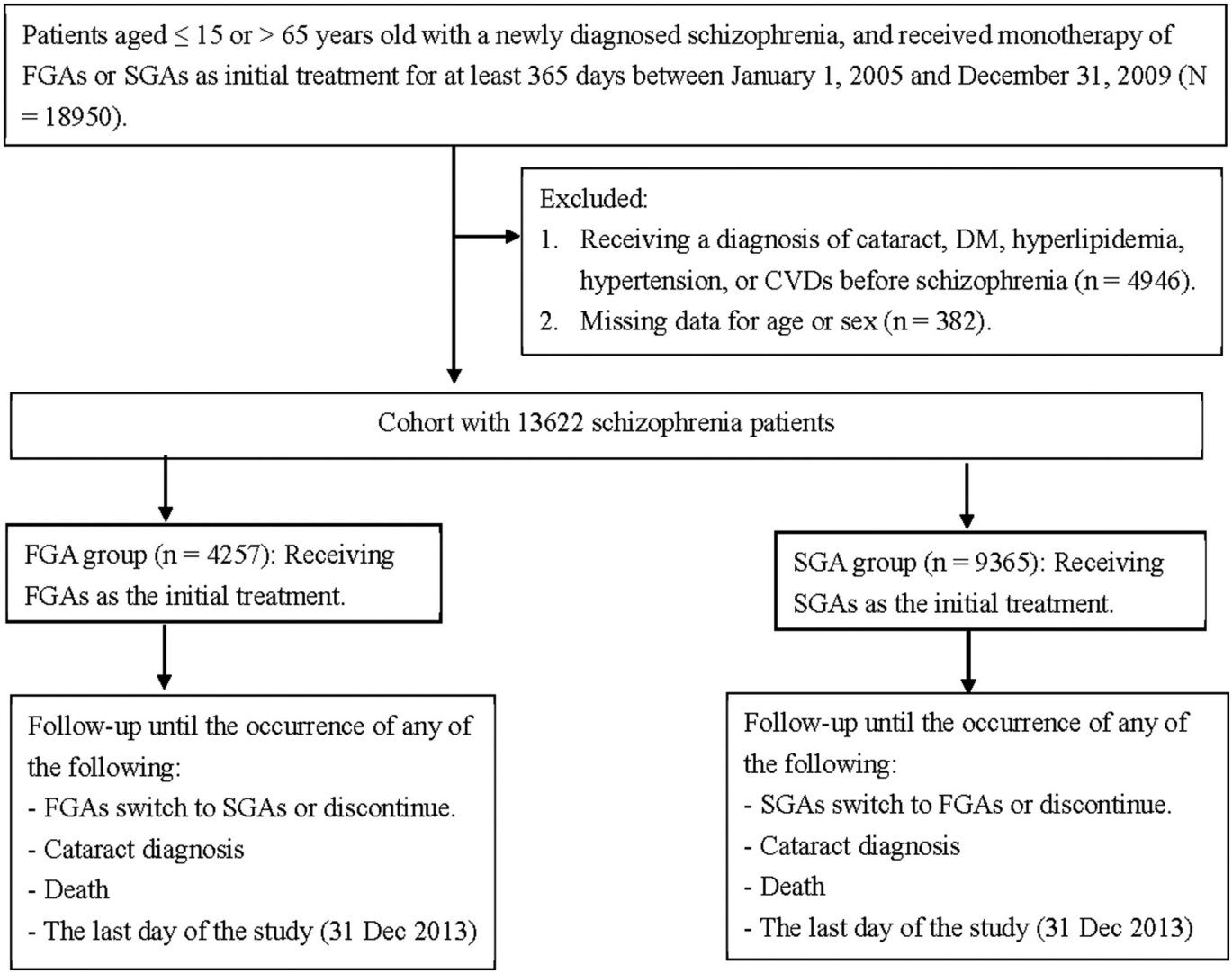

Fig. 1. presents the flowchart of study design and the process of patient selection.

or SGAs as initial treatment for at least 365 days. To ensure that the diagnoses were newly onset cataracts we excluded those who had received any diagnosis of cataract (ICD-9-CM code: 366) before the diagnosed schizophrenia ($n = 710$). We also excluded those who received any diagnosis of DM, hyperlipidemia, hypertension, or CVDs before schizophrenia ($n = 4236$) to diminish the potential risk of cataract contributed to these metabolic related diseases existing before antipsychotics. Additionally, patients with information regarding sex or age absent ($n = 382$) were also excluded. A total of 13,622 patients with schizophrenia were included in our study.

2.3. Outcome of interest

We identified all patients who received a cataract diagnosis (ICD-9-CM code 366) [excluding traumatic cataracts (ICD-9-CM code 366.2) and congenital cataracts (ICD-9-CM code 743.3)] at least twice in ambulatory claims or once in inpatient claims by an ophthalmologist during the follow-up period (Chu et al., 2017). In case of patients receiving a cataract diagnosis more than once, the date of the first cataract diagnosis was defined as the cataract diagnosis date.

2.4. Metabolism-related diseases definitions

Patients who received the following diagnosis at least twice in ambulatory claims or once in inpatient records during the study follow-up period were considered to have a metabolism-related disease: DM (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), hypertension (ICD-9-CM codes 401-405), or CVDs (heart disease: ICD-9-CM codes 410-429); and ischemic stroke (ICD-9-CM codes 433, 434, and 436) (Chen et al., 2012).

2.5. Antipsychotic exposure

Patients' exposure to antipsychotics was obtained from ambulatory and inpatient prescription claims data using the Anatomical Therapeutic Chemical Classification System code N05A (antipsychotics), but excluding N05AN (lithium) (Organization, 2014). We used dispensing data to estimate the number of prescription days. However, inpatient prescription data do not specify each day's dosage. Therefore, inpatient exposure to antipsychotics was estimated using the prescription days and defined daily dose in accordance with the World Health Organization Collaborating Centre for Drug Statistics Methodology (Organization and Organization, 2009).

Antipsychotics were divided into FGAs and SGAs according to the literature (Tandon et al., 2008). FGAs comprised chlorpromazine, levomepromazine, fluphenazine, perphenazine, prochlorperazine, trifluoperazine, thioridazine, pipotiazine, haloperidol, moperone, flupentixol, clopenthixol chlorprothixene, tiotixene, zuclopenthixol, pimozide, penfluridol, loxapine, sulpiride, and clothiapine. SGAs comprised amisulpride, aripiprazole, ziprasidone, clozapine, olanzapine, quetiapine, risperidone, zotepine, and paliperidone. Additionally, the literature showed that SGAs-induced metabolic changes markedly varied across medications (Allison and Casey, 2001; Gardner et al., 2005; Hirsch et al., 2017). Therefore, we categorized SGAs into high (clozapine and olanzapine), intermediate (quetiapine, risperidone, zotepine, and paliperidone), and low (amisulpride, aripiprazole, ziprasidone) metabolic risk categories to explore the impact of different drugs on the risk of cataract (Wu and Gau, 2015).

2.6. Covariates

Covariates that are known to be associated with cataract in patients with schizophrenia were also considered. We included the age at diagnosis, sex, use of steroid (yes/no), use of antidepressants (yes/no), and health services utilization during the follow-up period in the study.

The antidepressants use was defined as patients who exposure to the antidepressants over 365 days during the follow-up period (Erie et al., 2014). The antidepressants include the tricyclic antidepressants (amitriptyline, clomipramine, imipramine, dothiepin, doxepin, maprotiline, and melitracen), the selective serotonin reuptake inhibitors (fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, escitalopram), and the serotonin-norepinephrine reuptake inhibitors (venlafaxine, duloxetine, milnacipran) (Chou et al., 2017). In addition, we estimated health services utilization by calculating the yearly average number of outpatient, emergency room, and inpatient visits for each patient during the follow-up period (Saeedi et al., 2016).

2.7. Statistical analysis

Descriptive analyses and statistics were performed to compare baseline characteristics between patients receiving FGAs or SGAs. A *t*-test and chi-squared test were adopted for continuous variables and categorical variables, respectively. We categorized patients into FGA and SGA groups according to the initial treatment choice. Propensity score matching was adopted to balance observed age and sex differences between the FGA and SGA groups. Propensity scores indicate the probability that a patient received SGAs or FGAs based on their baseline characteristics. We defined the logic of the predicted probability of treatment as a propensity score using sex and the age at diagnosis. Patients receiving FGAs were matched on a 1:2 basis, with those receiving SGAs based on nearest-neighbor matching, and FGA and SGA patients were matched within their respective risk groups.

Cumulative function curves were generated to illustrate the cataract incidence. Cox hazard regression analyses with time-dependent covariates were adopted to estimate hazard ratios (HRs) of cataracts in patients receiving SGAs compared with patients receiving FGAs. DM, hyperlipidemia, hypertension, and CVDs that developed during follow-up were included as time-dependent variables. We used the Harrell's concordance index (C-index) to assess the prediction performance of the Cox hazard model (Harrell et al., 1996). To validate our main results, we conducted a stratified analysis to examine associations between antipsychotics and cataracts according to the status of DM and hyperlipidemia to prevent confounding effects from these variables.

All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA). The statistical significance of associations was assessed using $P < 0.05$. This study was reviewed and approved by the Institutional Review Board of Taipei Medical University (TMU-JIRB no. 201610013).

3. Results

Propensity score matching was performed to match patients with newly diagnosed schizophrenia considering age and sex. A resultant 3338 (33.3%) patients in the FGA group and 6676 (66.7%) patients in the SGA group were included (Table 1). The median follow-up was 4 years (interquartile range [IQR] = 5 years) from the diagnosis. The median time for developing cataracts was 4 years (IQR = 4 years) during the follow-up period. In origin cohort, patients receiving SGAs were significantly younger and more likely to be female than those receiving FGAs. The differences in sex and age substantially decreased after matching (Table 1). Patients who received SGAs had a higher percentage of antidepressants use and were more likely to develop cataracts and hyperlipidemia than those who received FGAs during the follow-up period (Table 2). Additionally, patients who developed DM and hyperlipidemia after receiving antipsychotics had 2.59-fold (95% CI = 1.52–4.44, $P < 0.01$) and 2.59-fold (95% CI = 1.50–4.47, $P < 0.01$) increased

Table 1
Baseline characteristics and who developed cataracts and metabolism-related diseases according to the type of antipsychotic used in the overall cohort and propensity-matched cohort.

	Overall cohort ($N = 13,622$)			Propensity-matched cohort ($N = 10,014$)		
	FGAs $n = 4257$	SGAs $n = 9365$	SD	FGAs $n = 3338$	SGAs $n = 6676$	SD
Age at diagnosis (years)						
Mean (STD)	37.8 (10.8)	34.4 (11.1)	0.44	35.3 (10.3)	35.2 (10.5)	0.01
Age group (years), *n* (%)						
35	1881 (44.2)	5453 (58.2)	0.81	1881 (56.4)	3808 (57)	0.04
36–45	1301 (30.6)	2226 (23.8)	0.49	874 (26.2)	1674 (25.1)	0.08
46–55	833 (19.6)	1261 (13.5)	0.64	424 (12.7)	848 (12.7)	0.00
56–65	242 (5.7)	425 (4.5)	0.33	159 (4.8)	346 (5.2)	0.13
Sex, *n* (%)						
Female	1864 (43.8)	4700 (50.2)	0.36	1677 (50.2)	3385 (50.7)	0.03
Male	2393 (56.2)	4665 (49.8)	0.36	1661 (49.8)	3291 (49.3)	0.03

SD (standardized mean difference) = |P1 − P2|/square root of [P1(1 − P1) + P2(1 − P2)/2]. They are the same for all categorical variables with 2 levels.
Abbreviations: STD, standard deviation; SD, standardized mean difference; FGAs, first-generation antipsychotics; SGAs, second-generation antipsychotics.

cataract risk over those who did not develop these diseases (Table 3).

Table 3 shows that the patients who received SGAs were associated with a 59% increase in the risk of cataracts compared with those receiving FGAs after adjusting for age at diagnosis, sex, steroid use, antidepressants use, health services utilization, year of diagnosis, and the status of DM, hyperlipidemia, hypertension, and CVDs (aHR, 1.59; 95% CI = 1.06–2.36, $P = 0.02$; C-index = 0.83). Additionally, compared with patients who received FGAs, those who received high-metabolic-risk SGAs were a significantly higher risk of cataracts after adjusting covariates (aHR 2.57; 95% CI: 1.35–4.88; C-index = 0.83). However, after adjusting for covariates, the risks of cataracts were not significantly higher in the group of low-and intermediate-metabolic-risks SGA when comparing with FGAs.

To understand the effect of metabolism-related diseases on the relationship between antipsychotics and cataract risks, we conducted a stratified analysis according to the status of DM and hyperlipidemia (Table 4). The cataract risk was higher in SGA groups compared with FGA groups in all strata. However, significant increases in the cataract risk were observed among patients without DM, and a borderline significant risk was observed among patients without hyperlipidemia.

Table 2
Percentage of patients with schizophrenia who developed cataracts and metabolism-related diseases according to the type of antipsychotic used in the propensity score-matched cohort ($N = 10,014$).

	FGAs $n = 3338$	SGAs $n = 6676$	*P*-value
Cataracts, *n* (%)			<0.01
No	3306 (99.04)	6567 (98.37)	
Yes	32 (0.96)	109 (1.63)	
Steroids use, *n* (%)			0.18
No	3007 (90.08)	5956 (89.22)	
Yes	331 (9.92)	720 (10.78)	
Antidepressants use, *n* (%)			<0.01
No	3131 (93.9)	6003 (89.9)	
Yes	204 (6.1)	673 (10.1)	
Health services utilization per year, mean (STD)[a]	15.6 (11.9)	16.1 (11.5)	0.05
Diabetes mellitus, *n* (%)			0.60
No	3233 (96.85)	6453 (96.66)	
Yes	105 (3.15)	223 (3.34)	
Hyperlipidemia, *n* (%)			<0.01
No	3211 (96.20)	6340 (94.97)	
Yes	127 (3.80)	336 (5.03)	
Hypertension, *n* (%)			0.49
No	3182 (95.33)	6384 (95.63)	
Yes	156 (4.67)	292 (4.37)	
Cardiovascular diseases, *n* (%)			0.44
No	3285 (98.41)	6556 (98.20)	
Yes	53 (1.59)	120 (1.80)	

Antidepressants include the tricyclic antidepressants, the selective serotonin reuptake inhibitors, and the serotonin-norepinephrine reuptake inhibitors.
Abbreviations: STD, standard deviation; FGAs, first-generation antipsychotics; SGAs, second-generation antipsychotics.
[a] Health services utilization was calculated the year average number of outpatient, emergency room, and inpatient visits for each patient during the follow-up period.

Table 3
Risk of cataracts associated with metabolism-related diseases and types of antipsychotic used in the propensity score-matched cohort ($N = 10,014$).

Variable	HR (95% CI)	aHR (95% CI)
Antipsychotics		
SGAs overall vs. FGAs	1.55 (1.05–2.31)	1.59 (1.06–2.36)[a]
SGA group by metabolic risk vs. FGAs		
Low-risk vs. FGAs	1.19 (0.57–2.49)	1.66 (0.78–3.52)[b]
Intermediate-risk vs. FGAs	1.69 (1.09–2.64)	1.49 (0.95–2.33)[b]
High-risk vs. FGAs	2.37 (1.27–4.46)	2.57 (1.35–4.88)[b]
Any combination of SGAs vs. FGAs	1.30 (0.80–2.10)	1.52 (0.93–2.48)[b]
Diabetes mellitus (DM)		
Yes vs. No	3.96 (2.55–6.15)	2.59 (1.52–4.44)[a]
Hyperlipidemia		
Yes vs. No	3.10 (2.02–4.75)	2.59 (1.50–4.47)[a]
Hypertension		
Yes vs. No	2.04 (1.24–3.35)	1.10 (0.63–1.91)[a]
Cardiovascular diseases (CVDs)		
Yes vs. No	2.36 (1.15–4.81)	1.27 (0.59–2.74)[a]

Low-metabolic-risk SGAs: amisulpride, aripiprazole, and ziprasidone.
Intermediate-metabolic-risk SGAs: quetiapine, risperidone, zotepine, and paliperidone.
High-metabolic-risk SGAs: clozapine and olanzapine.
Abbreviations: FGAs, first-generation antipsychotics; SGAs, second-generation antipsychotics; CI, confidence interval; HR, Hazard ratio; aHR, Adjusted hazard ratio; vs, versus.
[a] aHR was derived from the Cox hazard model including age at diagnosis, sex, steroid use, antidepressants use, health services utilization, year of diagnosis, exposure to antipsychotics (overall SGAs vs. overall FGAs) and time-dependent status of DM, hyperlipidemia, hypertension, and CVDs.
[b] aHR was derived from the Cox hazard model including age at diagnosis, sex, steroid use, antidepressants use, health services utilization, year of diagnosis, exposure to antipsychotics (low-, intermediate-, high-metabolic risk of SGAs vs. overall FGAs), and time-dependent status of DM, hyperlipidemia, hypertension, and CVDs.

Table 4
Adjusted hazard ratios (aHR) estimating cataract risk associated with second-generation antipsychotics (SGAs) compared with first-generation antipsychotics (FGAs) stratified in terms of diabetes mellitus (DM) and hyperlipidemia in propensity-matched cohort ($N = 10{,}014$).

	Person-years	Incident cataracts *n*	Incidence rate per 1000	SGA versus FGA aHR[a] (95% CI)	*P*
Developed DM[a]					
FGAs	596	6	10.67	Reference	
SGAs	1294	15	11.59	1.70 (0.63–4.63)	0.30
Without DM[a]					
FGAs	12,136	26	2.14	Reference	
SGAs	26,821	94	3.50	1.66 (1.07–2.58)	0.02
Developed hyperlipidemia[b]					
FGAs	741	3	4.05	Reference	
SGAs	1878	17	9.05	2.90 (0.82–10.28)	0.10
Without hyperlipidemia[b]					
FGAs	11,991	29	2.42	Reference	
SGAs	26,237	92	3.51	1.54 (1.01–2.35)	0.04

[a] aHR was derived from the Cox hazard model considering hyperlipidemia, hypertension, and cardiovascular diseases (CVDs) as time-dependent covariates and adjusting for age at diagnosis, sex, steroid use, antidepressants use, health services utilization, and year of diagnosis.
[b] aHR was derived from the Cox hazard model considering DM, hypertension, and CVDs as time-dependent covariates and adjusting for age at diagnosis, sex, steroid use, antidepressants use, health services utilization, and year of diagnosis.

4. Discussion

To our knowledge, this is the first study to investigate the long-term cataract risk and its association with metabolism-related diseases in patients with schizophrenia receiving antipsychotics. In this 8-year population-based follow-up study, after adjusting for age, sex, steroid use, and status of DM, hyperlipidemia, hypertension, and CVDs, patients receiving SGAs were 59% more likely to develop cataracts than those receiving FGAs. Patients receiving high metabolic risk of SGAs were more than twice as likely to develop cataracts compared with those receiving FGAs. Furthermore, the development of DM and hyperlipidemia during follow-up was associated with an increased cataract risk.

Previous studies have shown inconsistent results when reporting the association between antipsychotics and cataracts. Some studies have shown that phenothiazine, quetiapine, olanzapine, clozapine, and paliperidone have the potential to increase cataract risks (Kim et al., 2010; Lehman et al., 2004; Shahzad et al., 2002; Valibhai et al., 2001). However, other studies have not reported a positive association between SGAs and cataracts (Chou et al., 2016; Pakzad-Vaezi et al., 2013; Souza et al., 2008). This discrepancy might have several causes. First, one study was limited by its cross-sectional design and inadequate sample size (Souza et al., 2008). Second, exposure to antipsychotics was measured for only 90 days before the index date (Chou et al., 2016; Pakzad-Vaezi et al., 2013), which might be too short to detect actual effects. Third, risk factors before the initiation of antipsychotics were not ruled out, especially DM, which may potentially affect the association between antipsychotic use and cataract risks (Chou et al., 2016; Pakzad-Vaezi et al., 2013; Souza et al., 2008). Most of these limitations were overcome in our study, and evidence was provided of an association between the long-term effects of SGAs on cataract risks in patients with schizophrenia.

The mechanism of antipsychotic-induced cataracts is unclear. The present findings showed that the high-metabolic-risk SGAs, clozapine and olanzapine, were positively associated with the risk of cataracts after adjusting for other covariates, especially the status of DM in the Cox hazard model. These findings supported the positive association between impaired glucose tolerance and cataract development reported previously (Tan et al., 2008). Recent studies showed that patients with incident schizophrenia receiving clozapine and olanzapine (Houseknecht et al., 2007; McEvoy et al., 2005) were more likely to develop impaired glucose homeostasis (Pillinger et al., 2017) and metabolic syndrome (Hirsch et al., 2017; Reist et al., 2007) than those receiving other antipsychotics. Additionally, the animal study explains that the cataracts are positively associated with hyperlipidemia, such as plasma total cholesterol and triglyceride (TsuTsUMI et al., 1999). Therefore, the risk for metabolic may play an important role in the association between SGAs and the risk of cataracts. Future research investigating the relationship among blood glucose, antipsychotics, and cataracts by lab values may help to clarify the relationships.

In this study, we observed that the development of DM and hyperlipidemia after antipsychotic therapy was associated with cataract development, but this association was not observed among those who developed hypertension or CVDs. DM and hyperlipidemia were found positively associated with the risk of cataract in epidemiological (Rotimi et al., 2003; Rowe et al., 2000) and long-term population-based cohort studies (Lindblad et al., 2008; Maralani et al., 2013). However, no consensus was reached in the relationship between hypertension, CVDs, and cataract risks (Poh et al., 2016; Wang et al., 2015). Our findings are consistent with current literature. In the stratified analysis, we found that the effects of SGAs on cataract risks were significant among patients who did not develop DM or hyperlipidemia during the follow-up period but not among those who developed DM or hyperlipidemia. The development of metabolism-related conditions after antipsychotic use demonstrates a modification effect on the association between SGAs and cataract risks. Our results suggest that the contribution of SGAs to cataract risks is higher when metabolism-related diseases are absent, but become nonsignificant after the development of DM or hyperlipidemia. Although cataracts may have developed before metabolism-related diseases were diagnosed, we cannot rule out the possibility that another mechanism induces cataracts. Future studies are warranted to further distinguish patients more likely to develop metabolism-related diseases and discover other potential causes of cataracts.

4.1. Strengths and limitations

Several strengths of this study are worth mentioning. First, this is a well-designed, large, population-based study with long-term follow-up. Only incident schizophrenia cases were included in the study, which prevented the results from being confounded by the disease duration and schizophrenia severity. Second, variables measured in the study were appropriately defined. Patients with a history of cataracts, DM, hypertension, CVDs, or hyperlipidemia before a schizophrenia diagnosis were excluded from the study.

Therefore, we could clarify the effect of SGAs on these outcomes. In addition, DM, hypertension, CVDs, and hyperlipidemia were modeled as time-dependent variables in the Cox hazard model, which encompassed changes in the disease status over time.

The present study had several limitations. First, this study was conducted using a claims database. We had no information on lab values of levels of glycemic, HbA1c, or lipid profiles; blood pressure; or body weight for diagnosing metabolic diseases. Further research using lab values to confirm the associations among metabolism-related diseases, antipsychotics, and cataract risks is suggested. Second, important lifestyle and behavioral factors contributing to the risk of cataracts, such as smoking and sunlight exposure, were unavailable. Potential influences of these factors on the risk of cataract cannot be ruled out. Third, antipsychotic use was captured from prescription records. As such, the compliance level is uncertain. Fourth, this is an observational study which we do not know the reason that FGAs or SGAs was prescribed to patients at the first place. However, a slit-lamp examination was not offered to patients routinely before antipsychotic treatment. Therefore, the chance of patients receiving FGAs or SGAs is unlikely to be associated with the status of their cataract. In addition, the mean age of patients in the FGAs and SGAs was 37.8 and 34.4 years old. Both groups were rather early for developing cataracts (Prokofyeva et al., 2013). Although we cannot rule out the possibility of under-diagnosed cataract at baseline, the chance should be rare and randomly distributed in the group of FGAs and SGAs. Finally, because our study population was 95% Han Chinese our results are unlikely to be confounded by ethnicity, but it does limit the generalizability of our results (Executive Yuan, 2016). Recent studies have revealed that patients in Taiwan with schizophrenia receiving SGAs had a lower risk of developing metabolic diseases compared with those in western Asian countries, the United States, and Canada (Bou Khalil, 2012; McEvoy et al., 2005). In addition, associations between metabolic diseases and cataract risks are well documented (Rowe et al., 2000). Therefore, it is likely that the ethnic population with a higher incidence of metabolic diseases have a higher cataract risk after receiving SGAs compared with the Taiwanese population. However, we did find that SGAs increased cataract risks in patients without metabolism-related diseases. The effects of SGAs on cataract development may vary by ethnicity. Further studies to examine the association between SGAs and cataract risks in other ethnic groups are warranted.

5. Conclusions

SGA treatment was associated with an increased cataract risk in patients with schizophrenia. This result strongly supports the Mount Sinai Conference recommendations that mental health care professionals should monitor the vision of patients with schizophrenia annually (Marder et al., 2004). Patients who received antipsychotics especially those with high-metabolic-risk SGAs should be referred to ophthalmology if the patients have visual symptoms as they may be due to cataract, or even retinopathy or glaucoma which have a higher prevalence in patients with schizophrenia. Furthermore, patients with DM and hyperlipidemia should closely monitor their diseases to prevent cataract formation.

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Author contributions

Su-Chen Fang, Cheng-Yi Huang, Yu-Hsuan Joni Shao: Conceptualization, formal analysis, original draft, and Ding-Lieh Liao, Chun-Chi Hsu: writing, review, and editing. Yu-Hsuan Joni Shao: Data curation, methodology, project administration, funding acquisition.

Compliance with ethical standards

The authors declare that there are no conflicts of interest in relation to the participants of this study.

Ethical approval

This article does not include experiments on human participants.

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Declaration of competing interest

The authors declare that there are no conflicts of interest in relation to the participants of this study.

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