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Association of antipsychotic drugs on type 2 diabetes mellitus risk in patients with schizophrenia: a population-based cohort and in vitro glucose homeostasis-related gene expression study

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Abstract

Background Type 2 diabetes mellitus (T2DM) and its related complications are associated with schizophrenia. However, the relationship between antipsychotic medications (APs) and T2DM risk remains unclear. In this population-based, retrospective cohort study across the country, we investigated schizophrenia and the effect of APs on the risk of T2DM, and glucose homeostasis-related gene expression.

Methods We used information from the Longitudinal Health Insurance Database of Taiwan for individuals newly diagnosed with schizophrenia ($N=4,606$) and a disease-free control cohort ($N=4,606$). The differences in rates of development of T2DM between the two cohorts were assessed using a Cox proportional hazards regression model. The effects of APs on the expression of glucose homeostasis-related genes in liver and muscle cell lines were assessed using quantitative real-time PCR.

Results After controlling potential associated confounding factors, the risk of T2DM was higher in the case group than that in the control group [adjusted hazard ratio (aHR), 1.80, $p<0.001$]. Moreover, the likelihood of T2DM incidence in patients with schizophrenia without AP treatment (aHR, 2.83) was significantly higher than that in non-schizophrenia controls and those treated with APs (aHR ≤ 0.60). In an in vitro model, most APs did not affect the expression of hepatic gluconeogenesis genes but upregulated those beneficial for glucose homeostasis in muscle cells.

Conclusion This study demonstrates the impact of schizophrenia and APs and the risk of developing T2DM in Asian populations. Unmeasured confounding risk factors for T2DM may not have been included in the study. These findings may help psychiatric practitioners identify patients at risk of developing T2DM.

Keywords Schizophrenia, Antipsychotic medications, Type 2 diabetes mellitus, Cohort study, Glucose homeostasis

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Background

Schizophrenia is a brain disorder that can lead to persistent mental issues, but it is treatable, with a better prognosis in some cases. Approximately 1% of the global population suffers from this condition, which can affect social interactions and last for 30–50% of a person's life [1, 2]. Although it is treatable in some cases with a better prognosis, individuals with schizophrenia have a 12-fold higher mortality risk than the general population. Several factors, including somatic comorbidities, poor lifestyles, and a high rate of suicide, affect the complexity of schizophrenia [3]. Studies using clinical samples have indicated a strong correlation between schizophrenia and a higher prevalence of type 2 diabetes mellitus (T2DM), which may be related to medication, lifestyle choices, and gene-environment interactions [4].

Diabetes is a complex chronic disease that requires ongoing medical attention and multiple risk-reduction measures. It affects approximately 422 million individuals worldwide, most of which reside in low- and middle-income countries, and the disease is directly responsible for 1.5 million deaths annually. The incidence and prevalence of diabetes have steadily increased over the past few decades [5]. Diabetes is also associated with other consequences such as blindness, kidney failure, heart attacks, strokes, and lower limb amputations. Therefore, implementing interventions that promote the knowledge, skills, and abilities to prevent, detect, and effectively manage diabetes is crucial to reduce the rates of mortality and morbidity associated with diabetes as well as schizophrenia [5].

The prevalence of T2DM in individuals with schizophrenia depends on several factors, including methodological perspectives between studies, demographic disparities, genetics, and lifestyles. However, the prevalence of T2DM is 2–5 times higher in a population comprising individuals with schizophrenia than that in a general population [6]. A systemic report revealed that, the prevalence of T2DM was estimated to range from 5 to 22%, depending on the psychiatric disorder [7]. Development of T2DM in the general population and people with schizophrenia involves several common factors, such as sedentary lifestyle, obesity, advanced age, hypertension, hyperlipidemia, smoking, inactivity, poor diet, social determinants, poverty, poor sleep, stress, and hypertension [1]. However, these factors are more frequently observed in individuals with schizophrenia. Therefore, assessing the factors contributing to excess hyperglycemia in individuals with schizophrenia is important.

Antipsychotic medications (APs) are the primary form of treatment for the core symptoms of schizophrenia, including auditory hallucinations and delusions. APs can be categorized as first-generation (FGAs or typical APs) or second-generation (SGAs or atypical APs) [8]. FGAs block the three primary pathways of the neurotransmitter dopamine, while SGAs have an affinity for dopamine and 5-HT_2 receptors, making them more selective for the mesolimbic system [8]. However, the negative effects of APs can accumulate over time and exert negative metabolic consequences that adversely affect the health of patients with schizophrenia. A meta-analysis revealed a 1.3-fold higher risk of T2DM in patients treated with SGAs than that in those treated with FGAs [9]. Another study found that patients with schizophrenia treated with SGAs or FGAs had a higher risk of developing T2DM than non-schizophrenia controls [adjusted hazard ratios (aHR), 1.32, 95% CI 1.01–1.75] [10]. In addition, a meta-analysis showed that the prevalence of T2DM was 2.1% among individuals who had never taken APs and 12.8% among those who had [11, 12]. In Taiwan, FGAs are more commonly used than SGAs, particularly for older patients with schizophrenia and found that the association of SGAs with a higher risk of T2DM (aHR, 1.82; Cox model) [10]. In contrast, a systematic assessment of 22 prospective randomized controlled studies found no differences in glycemic aberrations between the placebo and APs cohorts [13]. However, most studies that assessed drug efficacy did not include comparisons with the general population and had limited follow-up periods.

In mammals, maintenance of glucose homeostasis relies on the coordinated action of three counter-regulatory hormones: insulin, glucagon, and glucocorticoids. The liver plays a crucial role in regulating glucose homeostasis that maintains a precise balance between the production of glucose by the liver through gluconeogenesis and the consumption of glucose by peripheral tissues [14]. The key enzymes in the gluconeogenesis pathway are phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase). PEPCK catalyzes the first step in gluconeogenesis, converting oxaloacetate to phosphoenolpyruvate; its overexpression in rat models causes hyperglycemia, insulin resistance, and hyperinsulinemia. G6Pase plays a crucial role in releasing glucose from glucose-6-phosphate, which is the final product of glycogen degradation and a part of the gluconeogenesis pathway [14]. Therefore, PEPCK and G6Pase are considered potential therapeutic target for the treatment of T2DM.

The human insulin receptor (*IR*) gene on chromosome 19 contains 22 exons; the alternative splicing of exon 11 produces two isoforms, *IR-A* and *IR-B*, which differ by their C-termini and 12 amino acids [15]. Some studies have demonstrated a reduced *IR-A: IR-B* ratio in the adipocytes and skeletal muscles of individuals with diabetes [16]. In patients with T2DM, insufficient expression or translocation of glucose transporter 4 (GLUT4) to the

plasma membrane of peripheral cells prevents glucose uptake for cellular energy production. GLUT4, a primary glucose transporter in skeletal muscle, is significantly lower in patients with T2DM and those with significant insulin resistance [17]. Angiopoietin-like protein 4 (ANGPTL4), plays a direct role in controlling insulin sensitivity, lipid metabolism, and glucose homeostasis [18]. Studies have demonstrated the potency of ANGPTL4, the target gene of peroxisome proliferation activators (PPARs), as antidiabetic and lipid-lowering medications [19].

Until now, observational cohort studies comparing the prevalence of T2DM in patients with and without APs, particularly in Asian communities, are limited. Therefore, this study aimed to examine the relationship of schizophrenia, APs medications, and the risk of T2DM development. Additionally, we performed the analysis to a impact of FGAs and SGAs on the expression of the genes involved in glucose homeostasis. The findings of this study may help practitioners identify patients at risk of developing T2DM.

Materials and methods

Data source

In this study, we used the data from a sub-database of the National Health Insurance Research Database (NHIRD) known as the Longitudinal Health Insurance Database (LHID), which covers 2 million beneficiaries. NHIRD has been maintained by the Taiwanese government since 1995 to store the health information of almost the entire population in the country. Our study examined the correlation between schizophrenia and T2DM using patient registration data as well as in-patient and ambulatory care records. Disease diagnoses were categorized according to the International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification (ICD-9/10-CM). The NHIRD encrypts patients' personal information to protect their privacy. It also provides researchers with anonymized identification numbers connected to key claim information such as sex, date of birth, medical services used, and prescriptions. Therefore, patient consent was not required to access NHIRD. This study was approved by the Institutional Review Board of China Medical University Hospital Research Ethics Committee [CMUH104-REC2-115 (CR-8)], and Research Ethnics Committee of Taichung Tzu Chi Hospital (REC113-07).

Study population

Individuals diagnosed with schizophrenia, identified using ICD-9-CM code 295 and ICD-10-CM code F20, comprised the case group in this study. The control group consisted of non-schizophrenia controls. The study was conducted between 2000 and 2017. Patients who developed T2DM before enrollment in the study or those under 18 years of age were excluded. The index day for case patients was the date of their schizophrenia diagnosis, whereas, for control patients, a random date between 2000 and 2016 was selected. Case and control patients were matched using a propensity score matching method based on sex, age (index year), and comorbidities at a ratio of 1:1.

Main outcome and comorbidities

The primary focus of our investigation was T2DM, which was categorized using the ICD-9-CM code 250 and ICD-10-CM code E11. Individuals were censored at death, loss to follow-up, withdrawal from the insurance system, or the end of 2017, whichever came first. Several comorbidities were included in the adjustment to account for potential confounding factors. These included hyperlipidemia (ICD-9-CM code 272; ICD-10-CM code E78), sleep disorder (ICD-9-CM code 327.23, 780.51, 780.53, 780.57; ICD-10-CM code G47.0, G47.1, G47.3), coronary artery disease (CAD; ICD-9-CM code 410–414; ICD-10-CM code I20-I25), hypertension (ICD-9-CM code 401–405; ICD-10-CM code I10-I16), chronic kidney disease (CKD; ICD-9-CM code 585, 586; ICD-10-CM code N18), and obesity (ICD-9-CM code 278.0; ICD-10-CM code E66.09, E66.1, E66.8, E66.9, E66.01, E66.2).

Cell culture and chemicals

Purest-grade chemicals for each experiment were obtained from Sigma-Aldrich (St. Louis, Missouri, USA) and dissolved in dimethyl sulfoxide (DMSO) at the appropriate concentrations. The concentrations used were determined based on the highest achievable plasma or serum drug concentrations, and the liver toxicity of these APs has been previously examined and documented [20]. The final concentrations for each FGAs (chlorpromazine [0.844 μM], chlorprothixene [1.450 μM], clothapine [0.465 μM], droperidol [0.226 μM], flupentixol [0.010 μM], fluphenazine [0.020 μM], haloperidol [0.027 μM], levomepromazine [2.435 μM], loxapine [0.029 μM], pimozide [0.041 μM], prochlorperazine [0.013 μM], sulpiride [1.180 μM], thioridazine [0.540 μM], and trifluoperazine [0.006 μM]) and SGAs (amisulpride [1.611 μM], aripiprazole [0.468 μM], brexpiprazole [0.323 μM], clozapine [2.359 μM], lurasidone [0.076 μM], olanzapine [0.256 μM], paliperidone [0.141 μM], quetiapine [0.985 μM], risperidone [0.027 μM], ziprasidone [0.310 μM], and zotepine [0.059 μM]) were used for the in vitro experiments. HepaRG™ (accession number: HPRGC10) human hepatoma cells were purchased from Thermo Fisher Scientific (Waltham, MA, USA), thawed, and kept alive for two weeks in Williams' E medium

(Sigma-Aldrich) supplemented with 10% FetalClone™ III serum, 1 × L-glutamine, 5 μg/mL human insulin, and 50 μM hydrocortisone hemisuccinate, without antibiotics. The medium was then replaced with the same medium supplemented with 2% DMSO for an additional two weeks to induce the cells to exhibit differentiated hepatocyte-like characteristics. Human rhabdomyosarcoma (RD, BCRC number: 60113) cell lines were maintained in Dulbecco's modified Eagle medium (DMEM). The cells were cultured at 37 °C in a 5% CO_2 humidified atmosphere. An acid phosphatase assay (ACP) based on *p*-nitrophenyl phosphate hydrolysis was performed to assess cell viability [21].

RNA isolation and quantitative real-time PCR (qRT-PCR)

Total RNA was extracted from differentiated HepaRG™ and RD cells using the Direct-zol™ RNA MiniPrep kit (ZYMO Research, Irvine, CA, USA), according to the manufacturer's instructions. RNA quality and quantity were determined by calculating the absorbance at 260/280 nm. cDNA was synthesized from 1 μg of total RNA using a MultiScribe™ reverse transcriptase kit (Thermo Fisher Scientific). We performed qRT-PCR using the StepOnePlus™ Real-Time PCR System and Luminaris Color HiGreen qPCR Master Mix (Thermo Fisher Scientific) to measure the expression of hepatic *G6Pase*, *PEPCK*, muscular *IR-A*, *IR-B*, *GLUT4*, and *ANGPTL4*. The primers used for qRT-PCR analysis are listed in Supplemental Table 1. The target cDNA concentration in each sample was calculated using the fractional PCR threshold cycle (Ct). Relative mRNA levels of the target genes were normalized to that of β-actin (*Actb*) and quantified using the following formula: $2^{-(Ct_{target\ gene} - Ct_{Actb})}$. The results are presented as fold-changes compared to the expression levels in the control group. Values were normalized to the expression of *Actb* with *Actb* expression levels in DMSO-treated cells set to 1.

Statistical analysis

Sex, age, and comorbidities were compared using chi-square and two-sample t-tests. The incidence rate was calculated by dividing the number of events by 1,000 person-years. The Cox proportional hazards model and Bonferroni adjustment for multiple comparisons was used to estimate the hazard ratios (HR) and determine the relationship between schizophrenia and T2DM. HR were adjusted for sex, age, and comorbidities. The Kaplan–Meier curves of patients with T2DM with and without schizophrenia were analyzed using the log-rank test. SAS software, version 9.4, was used for all statistical analyses, and a *p* value of less than 0.05 was considered statistically significant. For in vitro studies, the mean with standard error (SE) was reported for various measurements. Analysis of variance followed by Least Significant Difference test were performed for multiple comparisons. All *p* values were computed with reference to the vehicle control group, as shown in the figures. Experimental statistical analyses were performed using SPSS for Windows (version 20.0; IBM Corp., Armonk, N.Y.). A *p* value of 0.05 was used as the threshold for statistical significance.

Results

Baseline characteristics: demographic and association findings

The cohort under investigation comprised 4,606 individuals in the case and control groups each. The number of males in both groups was higher than that of the females; however, they did not show significant differences. The mean age of the participants in both groups was 37.6 and 37.9 years, respectively, and most were below 34 years. Moreover, patients with schizophrenia had a higher incidence of sleep disorder, hypertension, and obesity. In the case group, 82.9% received FGAs treatment, and 48.2% received SGAs treatment (Table 1).

Table 2 indicates that individuals with schizophrenia have a higher likelihood of developing T2DM than non-schizophrenia controls, with an adjusted HR (aHR)

Table 1 Demographic characteristics, comorbidities, and medications in patient with and without schizophrenia

Variable	Schizophrenia		*P* value
	No	Yes	
	N = 4,606	*N* = 4,606	
Sex	N (%)	N (%)	0.99
Female	2181 (47.4)	2181 (47.4)	
Male	2425 (52.7)	2425 (52.7)	
Age, mean (SD)	37.6 (12.9)	37.9 (12.3)	0.25
Stratify age			0.03
≤ 34	2300 (49.9)	2221 (48.2)	
35–49	1547 (33.6)	1665 (36.2)	
≥ 50	759 (16.5)	720 (15.6)	
Comorbidities			
Hyperlipidemia	954 (20.7)	932 (20.2)	0.57
Sleep disorder	1531 (33.2)	2536 (55.1)	0.001
Coronary artery disease (CAD)	482 (10.5)	494 (10.7)	0.68
Hypertension	1017 (22.1)	1119 (24.3)	0.01
Chronic kidney disease (CKD)	136 (2.95)	162 (3.52)	0.13
Obesity	59 (1.28)	119 (2.58)	0.001
Medications			
First generation antipsychotics (FGAs)		3820 (82.9)	
Second generation antipsychotics (SGAs)		2221 (48.2)	

Chi-Square Test; #: Two sample T-test

of 1.80 [95% confidence interval (CI) = 1.60–2.02]. This finding was also supported by the cumulative incidence curve shown in Fig. 1. Additionally, female patients with schizophrenia had a higher aHR for T2DM (1.98; 95% CI = 1.67–2.36) than male patients with schizophrenia (1.63; 95% CI = 1.38–1.91). Individuals with schizophrenia below the age of 34 years had a significantly increased risk of T2DM (aHR, 2.81; 95% CI = 2.22–3.56) compared to non-schizophrenia controls. For patients aged 35–49 years, the aHR for T2DM in the case group relative to that in the control group was 1.67 (95% CI = 1.40–2.00). The aHR of T2DM for patients with schizophrenia without any comorbidities (2.26; 95% CI = 1.80–2.83) was higher than that in patients with any one of the comorbidities (1.50; 95% CI = 1.31–1.71).

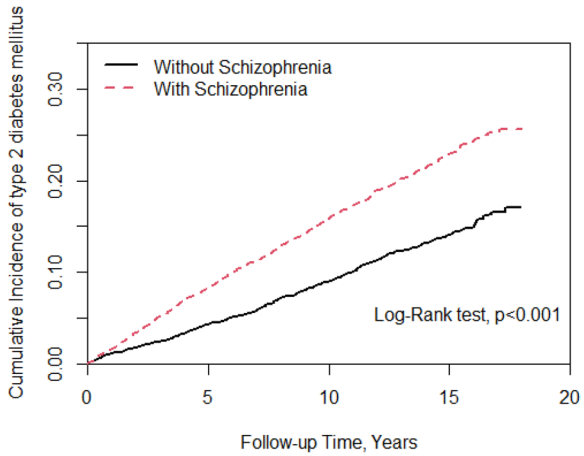

Fig. 1 Comparison of the cumulative incidence of type 2 diabetes mellitus (T2DM) in patients with and without schizophrenia using Kaplan–Meier curve analysis

The association between schizophrenia and T2DM in patients receiving medical treatment is shown in Table 3. Patients in the case group without any treatments, with FGAs, with SGAs, and with both FGAs and SGAs had an increased risk of T2DM [aHR, 2.83, 95% CI = 2.24–3.59; 1.73, 1.53–1.95; 1.71, 1.22–2.40; and 1.72, 1.53–1.94, respectively] than those in the control group. However, compared to the patients in the case group without any treatments, the risk of T2DM was reduced in patients treated with FGAs (aHR, 0.61; 95% CI = 0.48–0.77), SGAs (0.60; 95% CI = 0.40–0.88), or both FGAs and SGAs (0.68; 95% CI = 0.48–0.77).

The association between schizophrenia and T2DM in obese and non-obese patients who received medical treatment is shown in Table 4. In non-obese patients in the case group without any treatments, those treated with FGAs, with SGAs, and with both FGAs and SGAs had an increased risk of T2DM [aHR, 2.66, 99% CI = 1.92–3.67; 1.75, 1.49–2.05; 1.61, 1.01–2.56; and 1.73, 1.48–2.04, respectively] compared with those in the control group; however, compared with the patients in the case group without any treatments, the risk of T2DM

Table 2 Comparison of incidence and hazard ratio of type 2 diabetes mellitus (T2DM) stratified by sex, age, and comorbidities between with and without schizophrenia

Variable	Schizophrenia							
	No			Yes				
	Event	PY	Rate#	Event	PY	Rate#	Crude HR (95% CI)	Adjusted HR† (95% CI)
All	475	48,075	9.88	755	43,793	17.2	1.75 (1.56, 1.96)***	1.80 (1.60, 2.02)***
Sex								
Female	210	22,399	9.38	374	20,332	18.4	1.97 (1.66, 2.33)***	1.98 (1.67, 2.36)***
Male	265	25,676	10.3	381	23,462	16.2	1.58 (1.35, 1.85)***	1.63 (1.38, 1.91)***
Stratify age								
≤ 34	102	24,825	4.11	284	22,382	12.7	3.12 (2.49, 3.91)***	2.81 (2.22, 3.56)***
35–49	202	16,801	12.0	310	15,883	19.5	1.64 (1.37, 1.96)***	1.67 (1.40, 2.00)***
≥ 50	171	6448	26.5	161	5529	29.1	1.09 (0.88, 1.35)	1.16 (0.93, 1.45)
Comorbidity‡								
No	128	22,508	5.69	187	12,512	15.0	2.62 (2.09, 3.28)***	2.26 (1.80, 2.83)***
Yes	347	25,567	13.6	568	31,281	18.2	1.35 (1.18, 1.54)***	1.50 (1.31, 1.71)***

Rate#, incidence rate, per 1,000 person-years; Crude HR, crude hazard ratio.

Adjusted HR†: multivariable analysis including age, sex, and comorbidities of hyperlipidemia, sleep disorder, coronary artery disease, hypertension, and chronic kidney disease.

Comorbidity‡: Patients with any one of the comorbidities hyperlipidemia, sleep disorder, coronary artery disease, hypertension, chronic kidney disease, and obesity were classified as the comorbidity group.

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Table 3 Incidence, crude, and adjusted hazard ratio of type 2 diabetes mellitus (T2DM) compared among patients with schizophrenia with and without antipsychotic medications (APs) compared to non-schizophrenia controls

Variables	*N*	Event	PY	Rate[#]	Crude HR(95% CI)	Adjusted HR[†] (95% CI)	Adjusted HR[†] (95% CI)
Non-schizophrenia controls	4606	475	48,075	9.88	1 (Reference)	1 (Reference)	
Schizophrenia without APs treatment	466	83	2974	27.9	2.89 (2.29, 3.66)***	2.83 (2.24, 3.59)***	1 (Reference)
Schizophrenia with APs treatment							
FGAs	3820	636	38,579	16.5	1.67 (1.48, 1.88)***	1.73 (1.53, 1.95)***	0.61 (0.48, 0.77)***
SGAs	313	36	2204	16.3	1.69 (1.21, 2.38)**	1.71 (1.22, 2.40)***	0.60 (0.40, 0.88)**
Both	4140	672	40,820	16.5	1.67 (1.49, 1.88)***	1.72 (1.53, 1.94)***	0.68 (0.48, 0.77)***

Rate[#], incidence rate, per 1,000 person-years; Crude HR, crude hazard ratio

Adjusted HR[†]: multivariable analysis including age, sex, and comorbidities of hyperlipidemia, sleep disorder, coronary artery disease, hypertension, chronic kidney disease, and obesity

FGAs First generation antipsychotics, *SGAs* Second generation antipsychotics

**$P < 0.01$; ***$P < 0.001$

Table 4 Incidence, crude, and adjusted hazard ratio of type 2 diabetes mellitus (T2DM) compared among patients with schizophrenia with and without antipsychotic medications (APs) compared to non-schizophrenia controls

Variables	Crude HR (99% CI)	Adjusted HR† (99% CI)	Adjusted HR† (99% CI)
Non-schizophrenia controls	1 (Reference)	1 (Reference)	
Schizophrenia without APs treatment	2.89 (2.13, 3.94)*	2.83 (2.08, 3.87)*	1 (Reference)
Schizophrenia with APs treatment			
FGAs	1.67 (1.43, 1.95)*	1.73 (1.47, 2.02)*	0.61 (0.45, 0.83)*
SGAs	1.69 (1.08, 2.64)*	1.71 (1.09, 2.67)*	0.60 (0.36, 0.99)*
Both	1.67 (1.43, 1.95)*	1.72 (1.47, 2.01)*	0.60 (0.45, 0.83)*
Obesity = 0			
Non-schizophrenia controls	1 (Reference)	1 (Reference)	
Schizophrenia without APs treatment	2.75 (1.99, 3.78)*	2.66 (1.92, 3.67)*	1 (Reference)
Schizophrenia with APs treatment			
FGAs	1.68 (1.43, 1.97)*	1.75 (1.49, 2.05)*	0.66 (0.48, 0.91)*
SGAs	1.62 (1.02, 2.57)*	1.61 (1.01, 2.56)*	0.60 (0.35, 1.03)
Both	1.67 (1.43, 1.96)*	1.73 (1.48, 2.04)*	0.65 (0.48, 0.90)*
Obesity = 1			
Non-schizophrenia controls	1 (Reference)	1 (Reference)	
Schizophrenia without APs treatment	5.05 (1.56, 16.4)*	7.30 (1.92, 27.9)*	1 (Reference)
Schizophrenia with APs treatment			
FGAs	0.95 (0.42, 2.13)	1.20 (0.50, 2.87)	0.15 (0.04, 0.54)*
SGAs	2.60 (0.51, 13.3)	4.09 (0.68, 24.4)	0.44 (0.06, 3.31)
Both	1.02 (0.46, 2.25)	1.25 (0.53, 2.96)	0.15 (0.04, 0.57)*

Rate, incidence rate, per 1,000 person-years; Crude HR, crude hazard ratio

Adjusted HR†: multivariable analysis including age, sex, and comorbidities of hyperlipidemia, sleep disorder, coronary artery disease, hypertension, chronic kidney disease, and obesity

FGAs First generation antipsychotics, *SGAs* Second generation antipsychotics

*$P < 0.01$

was reduced in patients treated with FGAs (aHR, 0.66; 99% CI = 0.48–0.91) and those treated with both FGAs and SGAs (0.65; 99% CI = 0.48–0.90) or SGAs (aHR, 0.60, not significant). Obese patients in the case group without any treatments had an increased risk of T2DM (aHR, 7.30, 99% CI = 1.92–27.9); those treated with FGAs, with SGAs, and with both FGAs and SGAs had an increased risk of T2DM; however, the difference was not statistically significant. Compared with the patients in the case group without any treatments, the risk of T2DM was reduced in patients treated with FGAs (aHR, 0.15; 99% CI = 0.04–0.54) and in those treated with both FGAs and SGAs (0.15; 99% CI = 0.04–0.57) or SGAs (aHR, 0.44, not significant).

In vitro gene expression analysis

We used readily available FGAs (chlorpromazine, chlorprothixene, clothiapine, droperidol, flupentixol, fluphenazine, haloperidol, levomepromazine, loxapine, pimozide, prochlorperazine, sulpiride, thioridazine, and trifluoperazine) and SGAs (amisulpride, aripiprazole, brexpiprazole, clozapine, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone, and zotepine). We evaluated the toxicity of the APs by conducting cell viability experiments using HepaRG and RD cells. Concentrations of 0.844, 1.450, 0.465, 0.226, 0.010, 0.020, 0.027, 2.435, 0.029, 0.041, 0.013, 1.180, 0.540, and 0.006 μM for chlorpromazine, chlorprothixene, clothiapine, droperidol, flupentixol, fluphenazine, haloperidol, levomepromazine, loxapine, pimozide, prochlorperazine, sulpiride, thioridazine, and trifluoperazine. Concentrations of 1.611, 0.468, 0.323, 2.359, 0.076, 0.256, 0.141, 0.985, 0.027, 0.310, and 0.059 μM for amisulpride, aripiprazole, brexpiprazole, clozapine, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone, and zotepine. We evaluated the viability of the cells exposed to these APs for 72 h using the ACP test. Cell viability assessments using HepaRG and RD cells to evaluate the toxicity of the APs revealed no significant toxicity among those APs-treated cells (Supplemental Fig. 1).

Next, we measured the expression of *G6Pase* and *PEPCK* in differentiated HepaRG cells and those of *IR-A*, *IR-B*, *GLUT4*, and *ANGPTL4* in RD cells (Fig. 2A-G). Of the 14 FGAs tested here, 6 (droperidol, levomepromazine,

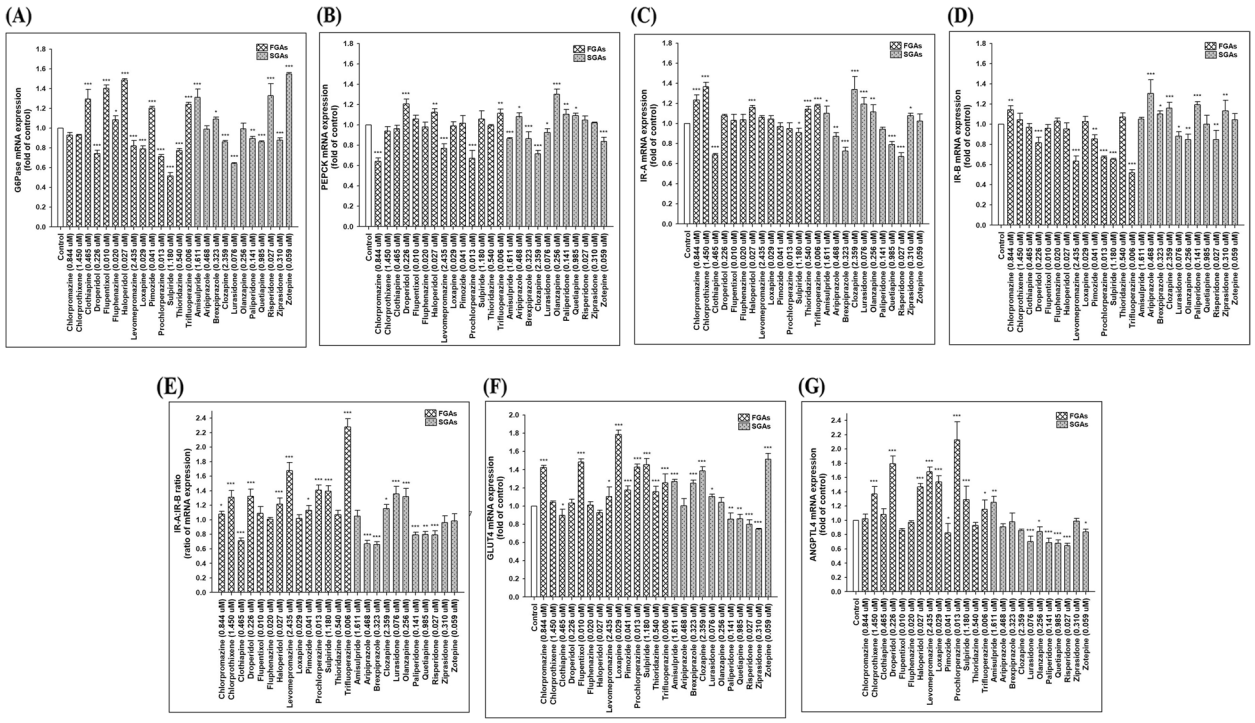

Fig. 2 Expression of glucose homeostasis-related genes in differentiated HepaRG and RD cells following treatment with antipsychotic medications (APs). Differentiated HepaRG cells (**A**, **B**) and RD cells (**C**, **D**, **E**, **F**, **G**) were treated for 72 h with FGAs [chlorpromazine (0.844 μM), chlorprothixene (1.450 μM), clothapine (0.465 μM), droperidol (0.226 μM), flupentixol (0.010 μM), fluphenazine (0.020 μM), haloperidol (0.027 μM), levomepromazine (2.435 μM), loxapine (0.029 μM), pimozide (0.041 μM), prochlorperazine (0.013 μM), sulpiride (1.180 μM), thioridazine (0.540 μM), and trifluoperazine (0.006 μM)] and SGAs [amisulpride (1.611 μM), aripiprazole (0.468 μM), brexpiprazole (0.323 μM), clozapine (2.359 μM), lurasidone (0.076 μM), olanzapine (0.256 μM), paliperidone (0.141 μM), quetiapine (0.985 μM), risperidone (0.027 μM), ziprasidone (0.310 μM), and zotepine (0.059 μM)]. Following treatment, RNA was extracted, and the expression levels of (**A**) G6Pase , (**B**) PEPCK , (**C**) IR-A , (**D**) IR-B , (**E**) IR-A: IR-B , (**F**) GLUT4 , and (**G**) ANGPTL4 were analyzed using quantitative reverse transcription-polymerase chain reaction. Values were normalized to the expression of Actb with Actb expression levels in dimethyl sulfoxide (DMSO)-treated cells set to 1. Results are expressed as means ± standard error (SE) ($n = 3$), * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ compared with cells treated with DMSO. G6Pase, glucose-6-phosphatase; PEPCK, phosphoenolpyruvate carboxykinase; IR-A/B, insulin receptor-α/−β; GLUT4, glucose transporter type 4; ANGPTL4, angiopoietin-like 4; FGAs, first-generation antipsychotic medications; SGAs, second-generation antipsychotic medications

loxapine, prochlorperazine, sulpiride, and thioridazine, 42.86%) and 3 (chlorpromazine, levomepromazine, and prochlorperazine, 21.43%) significantly reduced *G6Pase* and *PEPCK* expression in differentiated HepaRG and RD cells, respectively. Among the 11 SGAs, 5 (clozapine, lurasidone, paliperidone, quetiapine, and ziprasidone, 45.45%) significantly inhibited *G6Pase* expression, and 5 (amisulpride, brexpiprazole, clozapine, lurasidone, and zotepine, 45.45%) significantly reduced *PEPCK* expression (Fig. 2A-B). Two (chlorpromazine and chlorprothixene) and eight (chlorprothixene, clothiapine, flupentixol, fluphenazine, loxapine, pimozide, sulpiride, and thioridazine) FGAs did not affect the expression of *G6Pase* and *PEPCK*, respectively. In contrast, levomepromazine and prochlorperazine significantly decreased the expression of both *G6Pase* and *PEPCK*, whereas haloperidol and trifluoperazine induced their expression. Among the SGAs, clozapine and lurasidone reduced the expression of both genes in HepaRG cells (Fig. 2A-B).

We then investigated the expression of *IR-A*, *IR-B*, *GLUT4*, and *ANGPTL4* in RD cells and determined the *IR-A: IR-B* ratio. Nine of 14 FGAs (chlorpromazine, chlorprothixene, droperidol, haloperidol, levomepromazine, pimozide, prochlorperazine, sulpiride, and trifluoperazine) and 3 of 11 SGAs (clozapine, lurasidone, and olanzapine) increased the *IR-A: IR-B* ratio. In contrast, only one FGA (clothiapine) and five SGAs (aripiprazole, brexpiprazole, paliperidone, quetiapine, and risperidone) decreased them. Moreover, 28.57% of the tested FGAs ($n = 4$, flupentixol, fluphenazine, loxapine, and thioridazine) and 27.27% of the tested SGAs ($n = 3$, amisulpride, ziprasidone, and zotepine) did not affect the *IR-A: IR-B* ratio (Fig. 2C-E). Nevertheless, nine (chlorpromazine, flupentixol, levomepromazine, loxapine, pimozide, prochlorperazine, sulpiride, thioridazine, and

trifluoperazine) and eight (chlorprothixene, droperidol, haloperidol, levomepromazine, loxapine, prochlorperazine, sulpiride, and trifluoperazine) FGAs and five (amisulpride, brexpiprazole, clozapine, lurasidone, and zotepine) and one SGAs (amisulpride) significantly induced the expression of *GLUT4* and *ANGPTL4*, respectively (Fig. 2F-G). Four (paliperidone, quetiapine, risperidone, and ziprasidone) and five (lurasidone, paliperidone, quetiapine, risperidone, and zotepine) of eleven SGAs inhibited the expression of *GLUT4* and *ANGPTL4*, respectively (Fig. 2F-G). Overall, FGAs appeared to have a stronger inducing effect on these genes than SGAs. These findings suggest that AP therapy may improve blood glucose homeostasis in patients with schizophrenia by partially increasing the *IR-A: IR-B* ratio and affecting the expression of *GLUT4*, and *ANGPTL4*.

Discussion

Using the NHIRD, our study sought to elucidate the effect of APs on the risk of developing T2DM in Taiwanese patients with schizophrenia. After controlling for relevant factors, Taiwanese patients with schizophrenia had a 1.80-fold higher incidence of T2DM than the general population ($p < 0.001$). Notably, this population-based cohort study involves an extensive observation of an Asian population and identifies a statistically significant correlation between patients with schizophrenia and T2DM. Patients with schizophrenia who were not treated with APs had a significantly higher incidence of T2DM than the non-schizophrenia controls (aHR, 2.83; 95% CI, 2.24–3.59, $p < 0.001$). Moreover, patients with schizophrenia who were treated with APs had a significantly lower risk of developing T2DM than those who were not treated with APs (all aHR ≤ 0.60). By employing non-AP-treated patients with schizophrenia as the reference, we found that obese and non-obese patients treated with FGA alone or both FGA and SGA had a significantly lower risk of developing T2DM; however, this result was not found for those treated with SGA alone. Moreover, by evaluating the effects of APs on the expression of glucose homeostasis-related genes in HepaRG and RD cells, we found that most APs significantly reduced the expression of key gluconeogenesis-related genes (*G6Pase* and *PEPCK*). In contrast, most FGAs increased the *IR-A: IR-B* ratio and the expression of *GLUT4* and *ANGPTL4*, which may contribute to the reduction in T2DM incidence.

Schizophrenia is associated with a high prevalence of diabetes, especially in young, newly diagnosed patients who are not treated with APs. Therefore, schizophrenia itself may contribute to the risk of diabetes development [22]. Non-AP-treated patients with schizophrenia often experience unmanaged metabolic symptoms, increased stress, and HPA axis dysregulation. Metabolic abnormalities, such as insulin resistance and dyslipidemia, are commonly found in drug-naïve patients with schizophrenia, suggesting an intrinsic metabolic vulnerability tied to the disorder itself. These metabolic issues may be exacerbated by lifestyle factors, as untreated schizophrenia can reduce motivation for healthy behaviors [23]. Schizophrenia is associated with chronic stress and heightened HPA axis activity, leading to elevated cortisol levels even in the absence of APs. This persistent stress response promotes insulin resistance and weight gain, increasing the risk of diabetes [24]. Dysregulation of the HPA axis is a core feature of schizophrenia. Sustained activation of this axis increases cortisol production, contributing to impaired glucose metabolism and greater CVD risks [25]. In a meta-analysis, drug-naïve patients with schizophrenia were found to have higher insulin resistance and altered glucose metabolism than healthy controls, further supporting the notion that schizophrenia itself predisposes patients to metabolic issues, independent of medication [26]. Similarly, untreated schizophrenia is associated with increased stress levels and HPA axis dysfunction, resulting in elevated cortisol that worsens metabolic abnormalities, such as increased abdominal fat and glucose intolerance [27]. Collectively, these findings indicate that untreated schizophrenia is linked to a range of metabolic and stress-related issues and is largely due to unmanaged symptoms and HPA axis dysregulation.

Our patients were monitored for all comorbidities (including hyperlipidemia, sleep disorder, CAD, hypertension, CKD, and obesity) and follow ups were performed until the end of the study. Therefore, patients were monitored for comorbidities in all detection periods. Furthermore, obesity was extracted as an independent comorbidity in our study. Notably, the risk of T2DM was higher for non-obese patients with schizophrenia that were not treated with APs than non-obese patients with schizophrenia that were treated with APs, especially for those given FGAs and both FGAs and SGAs. However, obese patients with schizophrenia that were not treated with AP had a higher aHR of 7.30 (99% CI = 1.92–27.9). Adjusted HRs were not found to significantly differ between AP-treated patients with schizophrenia and the non-schizophrenia controls. By using patients with schizophrenia that were not treated with AP as a reference, we found a significantly lower risk of T2DM in obese and non-obese patients treated with FGA alone or both FGA and SGA; however, this result was not found for those treated with SGA alone. Therefore, obesity is recognized as a significant factor for the risk of T2DM development. Moreover, meta-analyses and other studies have shown that drug-naïve patients with schizophrenia have an elevated baseline risk for metabolic syndrome

(MetS), with this risk worsening with progression of the illness [11, 12, 28]. Despite having similar HbA1c levels to the controls, patients with schizophrenia often have compromised glucose homeostasis from disease onset, with elevated fasting glucose, post-oral glucose tolerance test levels, fasting insulin, and insulin resistance, which are exacerbated by illness progression [26]. Drug-naïve patients often have greater baseline weight, visceral fat, and laboratory markers of disrupted glucose and lipid metabolism. However, these prior studies provide limited insight into the long-term metabolic trajectory of non-AP-treated patients with schizophrenia [11, 12, 29, 30]. Therefore, the effect of untreated schizophrenia on long-term metabolic health remains unknown.

According to a noteworthy population-based case-control study, the risk of diabetes varies among patients treated with APs. Compared to untreated patients and those on conventional medications, patients administered drugs, such as olanzapine and clozapine, have a notably higher rate of diabetes, particularly younger patients; risperidone is also found to be associated with a significant risk of diabetes development [31]. According to some studies, no difference exists between FGAs and SGAs regarding diabetes risk; however, other studies indicate a slight but statistically significant increase in the risk of diabetes development with SGAs [9, 32]. Although weight gain is a well-known side effect of APs, patients without weight gain have been found to develop diabetes, suggesting the involvement of additional mechanisms, such as reduced anticholinergic-induced insulin production and disruptions in hypothalamic control of blood glucose levels due to dopamine antagonism [33]. However, the contribution of these mechanisms has not been proven. Of note, retrospective studies may not fully elucidate the role of APs in the risk of diabetes development due to methodological issues, such as cohort size, medication pre-exposure, and confounding factors, including varying schizophrenia subtypes, medication adherence, and follow-up periods. In addition, increased diabetes risk may not be unique to schizophrenia; other psychosis-spectrum disorders could share similar metabolic vulnerabilities. The use of a transdiagnostic approach in future research could clarify whether these risks are generalized across psychosis-related illnesses.

The metabolic risks associated with APs may result from their effects on several neurotransmitter receptors, including dopamine D_2 and D_3, histamine H_1, serotonin 5-HT_{2A} and 5-HT_{2C}, and muscarinic M_3 receptors in the central and peripheral nervous systems. These interactions can alter signaling in the HPA axis, leading to increased hunger, appetite, and subsequent weight gain. H_1 receptor antagonism affects the hypothalamic centers responsible for satiety, potentially causing hyperphagia [34]. Notably, the sedative effects of APs on H_1, M_1, and adrenergic 1 receptors can encourage sedentary behavior, further contributing to weight gain and diabetes risk [35]. Owing to these concerns, the American Diabetes Association and the American Psychiatric Association released guidelines in 2004, emphasizing regular monitoring of weight, waist circumference, blood pressure, fasting glucose, and lipid profiles for patients prescribed APs. Although AP-induced changes in dopamine and serotonin receptor function have been explored, the effects of APs on gene expression related to glucose homeostasis have not been thoroughly assessed. Understanding these gene expression changes is critical for preventing and managing T2DM in patients treated with APs. In the present study, AP-treated patients with schizophrenia were found to have a decreased risk of developing T2DM, potentially due to the modulation of genes related to glucose homeostasis. In particular, less than 40% of SGAs increased the expression of the gluconeogenic genes, *G6Pase* and *PEPCK*, by less than 1.5-fold relative to the controls, suggesting that APs may not play a major role in regulating these enzymes in the liver. As revealed using *PEPCK/G6Pase* knockout mice, which could not synthesize glucose and had impaired survival [36], these enzymes are essential for gluconeogenesis. Based on other studies, IR isoform distribution also affects glucose metabolism in patients with T2DM, resulting in increased IR-B levels and decreased IR-A levels in the skeletal muscle [37]. Compared with normal individuals, patients with T2DM had significantly lower percentages of IR-A, which has a 1.5-to 2-fold greater affinity for insulin than the IR-B isoform, in the femoral muscles. Reduced insulin action in patients with T2DM may be caused by altered splicing of IR-RNA, which favors low-affinity IR-B [38]. This alteration is associated with impaired insulin sensitivity and reduced glucose uptake. These findings are supported by those of our study, as most APs, particularly FGAs, were found to alter the *IR-A: IR-B* ratio, thereby potentially enhancing insulin sensitivity in patients with schizophrenia. The pathogenesis of T2DM is significantly influenced by *GLUT4* expression. In fact, reduced *GLUT4* levels or impaired translocation to the cell membrane hinders glucose entry into cells for energy production [17]. In the present study, 56% of the tested APs induced *GLUT4* expression, with some APs inducing more than a 1.5-fold increase relative to the controls, suggesting a metabolic benefit. The levels of *ANGPTL4*, which may contribute to improved glucose tolerance, were also increased. *ANGPTL4* is regulated by PPARγ, and its enhanced expression, especially in muscle cells, supports the management of T2DM by reducing hepatic glucose production [39]. Previously, *ANGPTL4* was found to improve glucose tolerance and reduce blood

sugar levels in diabetic mice [18]. Serum ANGPTL4 levels are typically lower in patients with T2DM and are inversely correlated with plasma glucose concentrations [39]. In the present study, FGAs led to a greater induction of *ANGPTL4* expression than SGAs, suggesting that AP-induced elevation of *ANGPTL4* may have therapeutic benefits in managing T2DM. This positive effect on glucose homeostasis suggests the potential role for APs in supporting metabolic health in patients with schizophrenia that are at risk of developing diabetes.

In this longitudinal population-based cohort study, we investigated the epidemiology of T2DM risk in Taiwanese patients with schizophrenia by comparing age- and sex-matched patients and controls. In addition, we determined the effects of APs on glucose homeostasis-related gene expression in cell models. Notably, this is the first study to evaluate the association between schizophrenia and the risk of T2DM in an Asian population. However, this study had several limitations. Although Taiwan's national health insurance system implements strict review mechanisms to minimize false positives, inaccuracies in insurance claims classification could impact data reliability. In addition, the NHIRD lacks personal health information on smoking, alcohol use, body mass index (BMI), lifestyle factors, and family history, which limits our ability to control for all potential confounders. Some data were anonymized, preventing direct patient contact and access to clinical specifics. T2DM severity could not be assessed using glucose or HbA1c levels. Moreover, our case definitions relied on diagnoses and treatment histories without any information on disease progression. Notably, methodological differences between studies hindered direct comparisons, and underdiagnosis of schizophrenia in Taiwan might impact the findings. Nevertheless, as APs are generally only prescribed to clinically diagnosed patients with schizophrenia in Taiwan, our data on AP use are closely linked to confirmed schizophrenia cases. This study had several strengths. A population-based cohort of patients and anonymized data were employed to reduce selection bias. The effects of schizophrenia and APs on the risk of developing T2DM were assessed over an extended follow-up period. Notably, factors that might influence the development of T2DM were controlled by adjusting for age and sex at a 1:1 ratio. Finally, despite the probability of detection bias occurring if the enrolled participants had more hospital visits than the control population, the incidence of T2DM remained 1.80-fold higher in patients with two hospital visits annually. Notably, non-AP-treated patients with schizophrenia had a significantly higher risk of T2DM, particularly if obese. Among non-obese patients with schizophrenia, those treated with APs, especially FGAs, had a reduced risk of T2DM compared to untreated individuals. In the obese schizophrenia group, patients treated with FGA alone or both FGA and SGA had a lower T2DM risk than those that were not treated with AP. Therefore, obesity is recognized to increase the risk of T2DM development in patients with schizophrenia. Treatment with APs, particularly FGAs, may mitigate this risk. Our findings align with the notion that AP-treated patients may receive more regular follow-up and better somatic care, which helps manage prediabetes and other risk factors of T2DM. Overall, these results emphasize the importance of comprehensive care for patients with schizophrenia, including careful management of AP treatment and attention to modifiable risk factors. Future studies, including prospective cohort studies and randomized controlled trials, that use alternative databases and more detailed patient information are needed to further elucidate the relationships between schizophrenia, APs use, and T2DM. Of note, educating healthcare providers on schizophrenia and related metabolic risks is essential for delivering optimal patient care.

Conclusion

To our knowledge, this study is the first to investigate the association between schizophrenia, APs, and the risk of T2DM and examine how APs influence glucose homeostasis-related gene expression. Patients with schizophrenia were found to have a higher risk of T2DM than the controls; however, those treated with APs had a lower risk than those that were not treated with APs. APs may have a positive influence on blood glucose control by modulating gene expression. To achieve effective diabetes management for these patients, careful AP treatment, a healthy lifestyle, and access to healthcare are critical. Furthermore, early diabetes diagnosis, antidiabetic treatments, and coordinated medical and psychiatric care can reduce diabetes risk, complications, and disparities in this population.

Abbreviations

ACP	Acid phosphatase
aHR	Adjusted hazard ratio
ADA	American Diabetes Association
APA	American Psychiatric Association
ANGPTL4	Angiopoietin-like protein 4
APs	Antipsychotic medications
CKD	Chronic kidney disease
CI	Confidence interval
CAD	Coronary artery disease
DMSO	Dimethyl sulfoxide
DMEM	Dulbecco's modified Eagle medium
FGAs	First-generation antipsychotics
GLUT4	Glucose transporter 4
G6Pase	Glucose-6-phosphatase
HPA	Hypothalamic pituitary adrenal
IR	Insulin receptor
ICD-9/10-CM	International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification
LHID	Longitudinal Health Insurance Database

MetS	Metabolic syndrome
NHIRD	National Health Insurance Research Database
PPARs	Peroxisome proliferation activators
PEPCK	Phosphoenolpyruvate carboxykinase
SGAs	Second-generation antipsychotics
SE	Standard error
T2DM	Type 2 diabetes mellitus

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
Author contributions Conceptualization, Y.-J.F., W.-Y.L., and Y.-P.L.; methodology, Y.-J.F., W.-Y.L., and Y.-P.L.; software, C.-L.L., Y.-C.C., and H.-H.H.; validation, H.-H.H., C.-H.C., and F.-J.T.; formal analysis, Y.-J.F., W.-Y.L., C.-L.L., Y.-C.C., and Y.-P.L.; investigation, Y.-J.F., W.-Y.L., and Y.-P.L.; resources, C.-L.L., N.T., and F.-J.T.; data curation, C.-L.L., Y.-C.C., and Y.-P.L.; writing—original draft preparation, all authors; writing—review and editing, all authors; visualization, all authors; supervision, Y.-J.F., W.-Y.L., and Y.-P.L.; project administration, Y.-J.F., W.-Y.L., and Y.-P.L.; funding acquisition, Y.-J.F., W.-Y.L., and Y.-P.L.

Data availability
The published publication contains all of the data that were created or examined during this investigation. Although institutional restrictions prevent data sharing from being made publicly available, the China Medical University Hospital may provide authorization to share data upon request.

Declarations

Ethics approval and consent to participate
The NHIRD encrypts the patients' personal information to protect their privacy. It also provides researchers with anonymized identification numbers connected to key claim information such as sex, date of birth, medical services used, and prescriptions. Therefore, patient consent was not required to access NHIRD. To satisfy the criteria for exemption, the China Medical University Institutional Review Board (IRB) issued a clearance [CMUH104-REC2-115 (CR-8)] and Research Ethnics Committee of Taichung Tzu Chi Hospital (REC113-07). The IRB Review Board waived the requirement for permission.

Competing interests
The authors declare no competing interests.

Consent for publication
Not applicable.

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