

Associations between antipsychotics and the risk of incident cardiovascular diseases in individuals with schizophrenia: a nested case–control study

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ABSTRACT

Background The association between antipsychotics and cardiovascular diseases (CVDs) remains significant yet unestablished, especially in Chinese populations.

Objective To investigate the risk of CVDs associated with antipsychotics among Chinese individuals with schizophrenia.

Methods We conducted a nested case–control study on individuals diagnosed with schizophrenia in Shandong, China. The case group included individuals diagnosed with incident CVDs between 2012 and 2020. Each case was randomly matched with up to three controls. We used weighted logistic regression models to assess the risk of CVDs associated with antipsychotics and restricted cubic spline analysis to explore the dose–response relationship.

Findings In total, 2493 cases and 7478 matched controls were included in the analysis. Compared with non-users, any antipsychotics use was associated with higher risk of any CVDs (weighted OR=1.54, 95% CI 1.32 to 1.79), with the risk mainly driven by ischaemic heart diseases (weighted OR=2.26, 95% CI 1.71 to 2.99). Treatments with haloperidol, aripiprazole, quetiapine, olanzapine, risperidone, sulpiride and chlorpromazine were associated with increased risk of CVDs. A non-linear dose–response relationship between dosage of antipsychotics and risk of CVDs was observed, with a sharp increase in risk in the beginning and then flattening out with higher doses.

Conclusions Use of antipsychotics was associated with increased risk of incident CVDs among individuals with schizophrenia, and the risk varied substantially among different antipsychotics and specific CVDs.

Clinical implications Clinicians should consider the cardiovascular risk of antipsychotics and choose the appropriate type and dose of drugs in the treatment of schizophrenia.

BACKGROUND

Cardiovascular diseases (CVDs) are the leading cause of death in China, accounting for up to 40% of all deaths.¹ Furthermore, CVDs are the primary cause of elevated risk of mortality among individuals with schizophrenia.² Studies have reported that the life expectancy of individuals with schizophrenia is reduced 15–20 years than the general population, with CVDs contributing 17.4% and 22.0% to this reduction in men and women, respectively.³

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Individuals with schizophrenia are at a higher risk for cardiovascular disease (CVD) morbidity and mortality than the general population.
- ⇒ Evidence from previous studies suggests that antipsychotics are associated with many cardiovascular events, such as myocardial infarction, atrial fibrillation and cerebrovascular accidents.

WHAT THIS STUDY ADDS

- ⇒ In this large-scale, nested case–control study, we observed statistically significant associations between use of antipsychotics and risk of incident CVDs among individuals with schizophrenia in China.
- ⇒ The strengths of the association varied by different types of antipsychotics and differed across specific cardiovascular adversities.
- ⇒ Furthermore, antipsychotics have a significant effect on the risk of CVDs in a non-linear dose-dependent pattern.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ This study analysed one of the largest samples of schizophrenia cohorts in China based on a longitudinal cohort.
- ⇒ Findings of this study have important implications for clinical management of individuals with schizophrenia undergoing treatment with antipsychotics.
- ⇒ The risk of CVDs should be thoroughly examined when initiating or tailoring antipsychotic therapies.
- ⇒ Specific types (eg, haloperidol, risperidone and quetiapine) and high cumulative doses of antipsychotics should be cautiously prescribed to individuals with schizophrenia, who may present higher risk of CVDs, especially cerebrovascular diseases and ischaemic heart diseases.

Multiple risk factors for the incidence of CVDs among individuals with schizophrenia have been suggested, including sedentary behaviour,⁴ tobacco use,⁵ metabolic-related diseases⁶ and antipsychotics use.⁷ Since chlorpromazine was introduced in



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clinical practice in the 1950s, antipsychotics have become the first-line option for treatment of schizophrenia, with proven efficiency in alleviating the core symptoms of schizophrenia.^{7,8} On the other hand, there is growing evidence indicating associations between antipsychotics and CVDs, such as acute myocardial infarction,⁹ atrial fibrillation¹⁰ and cerebrovascular accidents.¹¹

Findings on the associations between antipsychotics and CVDs are inconclusive. By mechanism, antipsychotics may directly affect the user's cardiovascular functions, resulting in cardiovascular adverse reactions such as prolongation of QT interval and arrhythmia.¹² In addition, antipsychotics may also indirectly increase the risk of CVDs, for example, by inducing obesity and other metabolic dysfunctions.¹³ On the other hand, studies have reported that antipsychotics may improve the survival of individuals with schizophrenia,¹⁴ including an observed reduction in deaths due to cardiovascular-related diseases.¹⁵ The 'antipsychotic paradox' of high cardiovascular risk but low mortality has attracted more attention.¹⁶ The reason for this antipsychotic paradox may be that the use of antipsychotics improves patients' adherence to cardiovascular medications, thereby reducing mortality risk due to CVDs.¹⁷ Hence, more evidence is needed to evaluate the potential cardiovascular risk of antipsychotics. It also remains to be disentangled if and how the associations differ by types of antipsychotics and groups of specific CVDs. Improved understanding of the risk of incident CVDs is crucial in order for psychiatrists to make decisions on prescriptions for antipsychotics among individuals with schizophrenia.

Apart from the controversies of previous evidence on the association between antipsychotics and CVDs, reliable findings among Chinese individuals with schizophrenia are lacking. With rapidly emerging public health burden of both schizophrenia and CVDs in China,^{18,19} it is crucial to explore the associations between antipsychotics and CVDs in Chinese populations to provide more references to clinical decision-makers.

Objectives

In this study, using a nested case-control design, we aimed (1) to explore the associations between antipsychotics use and CVDs in individuals with schizophrenia and (2) to assess the associations by different types and doses of antipsychotics as well as by different CVDs.

METHODS

Data sources

Individuals with schizophrenia were identified from the 'Shandong Multi-Center Healthcare Big Data Platform (SMCHBDP)' in Shandong Province, China. The SMCHBDP integrates information from multiple databases, such as the basic public health services, electronic medical records, medical insurance claims and cause of death registers. Multistage sampling process covering all 17 municipalities in Shandong Province was adopted to achieve representativeness of the source population. The sampling included both urban and rural populations, and the base cohort accounts for about 5% of the provincial population. More details about sampling have been described in other studies.^{20,21} In China, the basic public health services cover the management of individuals with schizophrenia and other severe mental illnesses diagnosed by licensed psychiatrists. Regular follow-ups are carried out to collect information on mental health and physical health conditions, social functioning, and history of treatment including medication use.²² Based on the SMCHBDP, we established a dynamic cohort of schizophrenia according to the 10th International Classification of Diseases

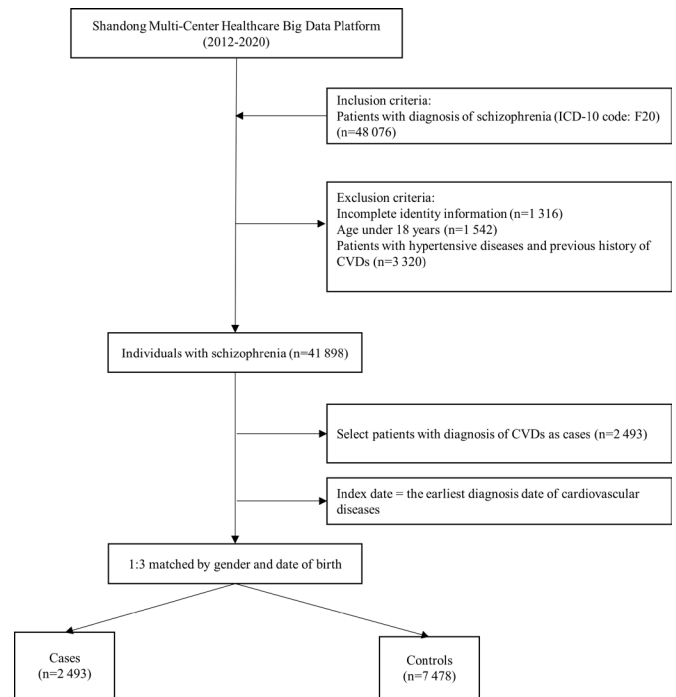


Figure 1 Flow chart demonstrating case and control selection. CVD, cardiovascular disease; ICD-10, 10th International Classification of Diseases.

(code: F20), which included 48 076 individuals with schizophrenia registered in the basic public health services between 1 January 2012 and 31 December 2020.

Study design and participants

We used a nested case-control design to investigate the associations between antipsychotics use and the risk of CVDs. Individuals receiving a diagnosis of incident CVDs (diagnostic codes are shown in online supplemental table S1) from 1 January 2012 to 31 December 2020 and over 18 years old at the time of first incident CVD (index dates) diagnosis were the case group. We randomly selected up to three matched controls using incidence density sampling from the same schizophrenia cohort with the same gender and date of birth as the case but without incident CVDs by index dates. In total, 2493 cases and 7478 controls were included in this study. A flow chart is presented in figure 1.

Exposure to antipsychotics

Antipsychotic exposure for each subject was determined from the basic public health services database and medical insurance database. The methods for assessing exposure to antipsychotics have been detailed in a previous literature.²¹ We defined the main exposure as having at least one record of antipsychotics use before the index date, dividing individuals with schizophrenia into users and non-users. Antipsychotics were first divided into the following: only use first-generation antipsychotics (FGAs; chlorpromazine, chlorprothixene, haloperidol, penfluridol, perphenazine, pipotiazine, sulphiride, zuclopenthixol and trifluoperazine), only use second-generation antipsychotics (SGAs; clozapine, aripiprazole, olanzapine, quetiapine, amisulpride, ziprasidone and risperidone) and combination use (FGAs and SGAs). The specific types of each antipsychotic medication were also analysed. We used the Anatomical Therapeutic Chemical classification/defined daily dose (DDD) system to assess the level of exposure to antipsychotics of each user (online supplemental

table S2) and converted the actual dose to cumulative defined daily doses (cDDD).²¹

Ascertainment of covariates

We collected information on other covariates from the database for the closest date before the index date as potential confounder. The covariates included the following: (1) Demographics data and lifestyle information were extracted from the basic public health services database, including age, gender, marital status, current residence, educational level, dietary and sleep quality, smoking, and drinking. Marital status was categorised into married and unmarried (single, divorced, widowed and unknown marital status). Current residence was classified into urban area and rural area. Educational level was classified into compulsory or intermediate education and tertiary education. Dietary and sleep quality were divided into well or general and poor according to individuals' self-reports. Smoking and drinking were defined as smoking at least one cigarette per day and drinking at least once a week, respectively. (2) Comorbidities were identified from electronic medical records and health check-up registers as binary variables, including physical comorbidities such as overweight or obesity, abdominal obesity, diabetes, dyslipidaemia, chronic obstructive pulmonary disease (COPD), peptic ulcer and cancer; and neuropsychiatric comorbidities such as depression, anxiety and dementia. Overweight or obesity was defined as body mass index ≥ 25 . Abdominal obesity was defined as waist circumference ≥ 102 cm for men and ≥ 88 cm for women. Other comorbidities were assessed by the medical records during the observation period (online supplemental table S3).

Statistical analysis

We compared the characteristics between the case and control groups by Student's t-test for continuous variables and χ^2 test for categorical variables, respectively. For measured potential confounders, we estimated the propensity scores of CVDs and

used weighted propensity scores to balance the distributions of confounders between the case and control groups.²³ Weighted logistic regression model (as the adjusted model, compared with the crude model without weight balancing) was then used to assess the risk of CVDs associated with antipsychotics use. Groups of antipsychotics (FGAs, SGAs and combination use) as well as some of the most commonly prescribed medications were analysed to test whether the strengths of associations varied. We carried out restricted cubic spline analysis to model the potential dose–response relationship between cumulative doses of antipsychotics and the risk of CVDs. Three knots were placed at the 75th, 85th and 95th percentiles, and 0 cDDD was used as the reference point.

We conducted subgroup analyses by gender and age group (≤ 65 years old, >65 years old) to evaluate the differential risk of CVDs in clinically relevant subpopulations. In addition, we investigated the associations with regard to selected types of specific CVDs according to the frequencies of outcomes: cerebrovascular diseases (I60–I69); ischaemic heart diseases (I20–I25); diseases of arteries, arterioles and capillaries (I70–I79); other forms of heart disease (I30–I52); diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified (I80–I89); and others (I00–I02, I05–I09, I26–I28, I95–I99).²⁴ We used R language (<https://www.R-project.org>) for data processing and analysis, specifically the 'glm' function to perform weighted logistic regression and the 'rms' package for restricted cubic spline analysis. $P < 0.05$ (two-sided) was considered statistically significant.

FINDINGS

Sample characteristics

A total of 2493 individuals with schizophrenia with CVDs diagnosed during follow-up and 7478 matched controls were included in this study. Descriptive characteristics are presented in table 1. Compared with the control group, the cases had a higher rate of comorbid physical conditions, such as overweight or obesity, diabetes, dyslipidaemia, COPD, peptic ulcer, cancer,

Table 1 Distribution of the unweighted sample and weighted sample

Characteristics	Unweighted sample* (n=9971)			Weighted sample† (n=3118.8)		
	Controls (n=7478)	Cases (n=2493)	Standardised mean difference	Controls (n=1559.4)	Cases (n=1559.4)	Standardised mean difference
Married, n (%)	5675 (75.9)	2032 (81.5)	0.138	1254.5 (80.4)	1254.5 (80.4)	<0.001
Urban, n (%)	2218 (29.7)	974 (39.1)	0.199	566.0 (36.3)	566.0 (36.3)	<0.001
Tertiary education, n (%)	36 (0.5)	34 (1.4)	0.092	14.6 (0.9)	14.6 (0.9)	<0.001
Poor dietary quality, n (%)	3472 (46.4)	1508 (60.5)	0.285	848.2 (54.4)	848.2 (54.4)	<0.001
Poor sleep quality, n (%)	2998 (40.1)	1472 (59.0)	0.386	807.4 (51.8)	807.4 (51.8)	<0.001
Smoking, n (%)	2138 (28.6)	936 (37.5)	0.191	524.3 (33.6)	524.3 (33.6)	<0.001
Drinking, n (%)	1315 (17.6)	738 (29.6)	0.286	396.0 (25.4)	396.0 (25.4)	<0.001
Overweight or obesity, n (%)	2181 (29.2)	805 (32.3)	0.068	493.0 (31.6)	493.0 (31.6)	<0.001
Abdominal obesity, n (%)	2256 (30.2)	843 (33.8)	0.078	503.8 (32.3)	503.8 (32.3)	<0.001
Diabetes, n (%)	693 (9.3)	534 (21.4)	0.342	253.8 (16.3)	253.8 (16.3)	<0.001
Dyslipidaemia, n (%)	1467 (19.6)	676 (27.1)	0.178	346.4 (22.2)	346.4 (22.2)	<0.001
COPD, n (%)	15 (0.2)	104 (4.2)	0.274	12.5 (0.8)	12.5 (0.8)	<0.001
Peptic ulcer, n (%)	42 (0.6)	295 (11.8)	0.481	34.7 (2.2)	34.7 (2.2)	<0.001
Cancer, n (%)	24 (0.3)	106 (4.3)	0.265	17.4 (1.1)	17.4 (1.1)	<0.001
Depression, n (%)	23 (0.3)	103 (4.1)	0.262	15.6 (1.0)	15.6 (1.0)	<0.001
Anxiety, n (%)	40 (0.5)	132 (5.3)	0.286	24.4 (1.6)	24.4 (1.6)	<0.001
Dementia, n (%)	9 (0.1)	33 (1.3)	0.142	6.2 (0.4)	6.2 (0.4)	<0.001

*Case and controls matched by age and gender.
†Proportions were weighted using overlap weighting.
COPD, chronic obstructive pulmonary disease.

Table 2 Associations between antipsychotics and risk of CVDs

Groups	Distribution		Risk of CVDs	
	Controls, n (%)	Cases, n (%)	Crude OR* (95% CI)	Weighted OR† (95% CI)
Overall				
Antipsychotics use‡				
Non-users	5730 (76.6)	1577 (63.3)	Ref	Ref
Users	1748 (23.4)	916 (36.7)	1.85 (1.68 to 2.03)	1.54 (1.32 to 1.79)
Type of antipsychotics				
Non-users	5730 (76.6)	1577 (63.3)	Ref	Ref
Only FGAs	549 (7.3)	276 (11.1)	1.79 (1.53 to 2.09)	1.51 (1.18 to 1.93)
Only SGAs	832 (11.1)	422 (16.9)	1.78 (1.57 to 2.03)	1.45 (1.18 to 1.78)
Combination	367 (4.9)	218 (8.7)	3.73 (3.41 to 4.08)	1.77 (1.34 to 2.36)
Men				
Antipsychotics use				
Non-users	2674 (75.6)	745 (63.2)	Ref	Ref
Users	862 (24.4)	434 (36.8)	1.77 (1.54 to 2.03)	1.54 (1.24 to 1.92)
Women				
Antipsychotics use				
Non-users	3056 (77.5)	832 (63.3)	Ref	Ref
Users	886 (22.5)	482 (36.7)	1.92 (1.69 to 2.19)	1.55 (1.26 to 1.93)
Age ≤65 years				
Antipsychotics use				
Non-users	3472 (75.1)	931 (60.4)	Ref	Ref
Users	1154 (24.9)	611 (39.6)	1.91 (1.69 to 2.15)	1.55 (1.28 to 1.89)
Age >65 years				
Antipsychotics use				
Non-users	2258 (79.2)	646 (67.9)	Ref	Ref
Users	594 (20.8)	305 (32.1)	1.74 (1.49 to 2.04)	1.52 (1.18 to 1.97)

*Crude OR adjusted for age and gender through matching.
†Weighted ORs were weighted using overlap weighting.
‡Antipsychotics use refers to ever treatment with antipsychotics during follow-up.
CVDs, cardiovascular diseases; FGAs, first-generation antipsychotics; Ref, reference; SGAs, second-generation antipsychotics.

depression, anxiety and dementia ($p < 0.001$). After overlap weighting, the measured confounders were well balanced between the cases and controls. Online supplemental figure S1 shows that the density distributions of propensity scores became almost fully overlapped after overlap weighting.

Any antipsychotics and risk of any CVDs

During follow-up, 26.7% of individuals with schizophrenia had taken antipsychotics before the index date, with the proportion significantly higher in the case group than in the control group (916 (36.7%) vs 1748 (23.4%), $p < 0.001$). Weighted logistic regression analyses showed a statistically elevated risk of CVDs in individuals with schizophrenia associated with any antipsychotics use (weighted OR=1.54, 95% CI 1.32 to 1.79). The associations were similar with regard to the direction and strengths when stratifying the analyses on gender and age (table 2).

Types of antipsychotics and risk of any CVDs

Regarding ever use of grouped antipsychotics, FGAs only (weighted OR=1.51, 95% CI 1.18 to 1.93), SGAs only (weighted OR=1.45, 95% CI 1.18 to 1.78) and combination use (weighted OR=1.77, 95% CI 1.34 to 2.36) were all associated with higher risk of CVDs as compared with non-users, with the combination group presenting the highest risk (table 2).

We further analysed the risk of any CVDs associated with relatively common specific antipsychotics in our cohort. Haloperidol (weighted OR=2.87, 95% CI 1.70 to 4.83) presented the

highest risk for CVDs among any antipsychotics, followed by aripiprazole, quetiapine, olanzapine, risperidone, sulpiride and chlorpromazine. Other antipsychotics including perphenazine, penfluridol, ziprasidone, clozapine and amisulpride were also used more often among cases than controls. Although the weighted ORs were not statistically significant, potentially elevated risk of CVDs cannot be ruled out (figure 2B).

Antipsychotics and specific CVDs

We investigated the associations with specific types of CVDs, including cerebrovascular diseases, ischaemic heart diseases, diseases of the arteries, etc. The group assignments and the corresponding frequencies are provided in online supplemental table S1. Weighted logistic regression showed that use of antipsychotics was associated with ischaemic heart diseases (weighted OR=2.26, 95% CI 1.71 to 2.99), but not statistically associated with other types of CVDs (figure 2A).

We then analysed specific antipsychotics and relatively more common types of CVDs, including cerebrovascular diseases and ischaemic heart diseases. Our results showed elevated risk of cerebrovascular disease (figure 2C) associated with ever use of haloperidol (2.53, 95% CI 1.10 to 5.81), quetiapine (2.20, 95% CI 1.06 to 4.56) and risperidone (1.71, 95% CI 1.14 to 2.54). When looking at ischaemic heart diseases (figure 2D), increased risks were observed in ever use of haloperidol (3.31, 95% CI 1.45 to 7.57), sulpiride (3.35, 95% CI 1.55 to 7.22), risperidone (2.61, 95% CI 1.68 to 4.05), quetiapine (2.41, 95% CI

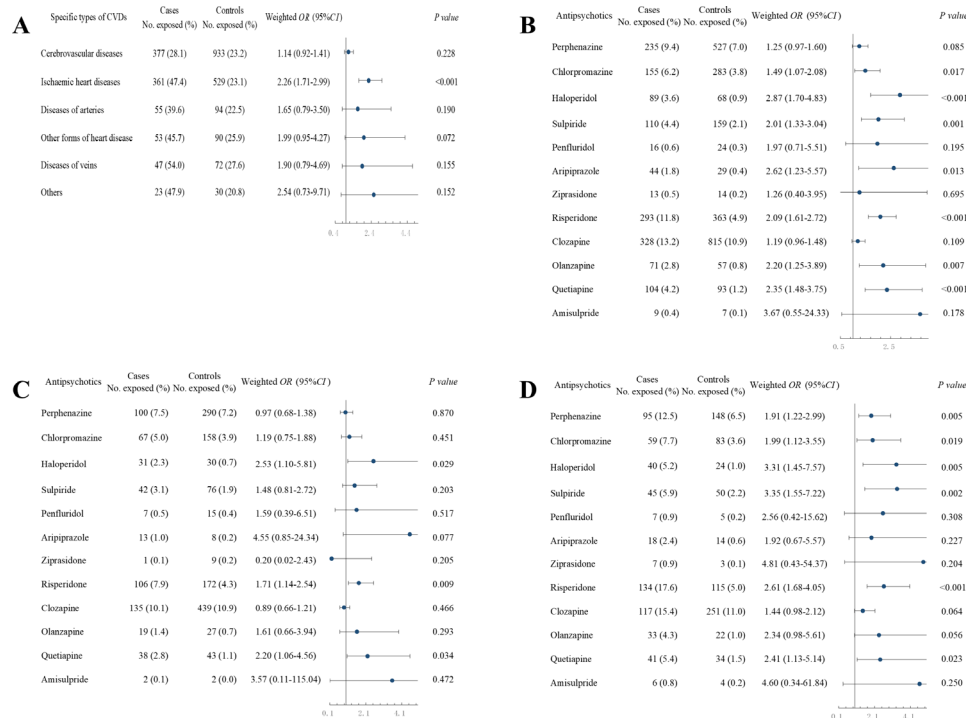


Figure 2 Associations between use of specific antipsychotics and specific types of CVDs. (A) Associations between any antipsychotic use and risk of specific types of CVDs. (B) Associations between specific antipsychotics and all CVDs. (C) Associations between specific antipsychotics and cerebrovascular diseases. (D) Associations between specific antipsychotics and ischaemic heart diseases. CVDs, cardiovascular diseases.

1.13 to 5.14), chlorpromazine (1.99, 95% CI 1.12 to 3.55) and perphenazine (1.91, 95% CI 1.22 to 2.99). Statistical power was limited when analysing other antipsychotics.

Dose–response relationship between antipsychotics and risk of CVDs

As shown in figure 3A, the risk of CVDs increased in proportion to elevation in cumulative doses of antipsychotics, up to an inflection point of around 500 cDDD, where the slope of the relationship was attenuated (p value for non-linearity <0.001; p value for overall trend <0.001). There was also a non-linear dose–response relationship between risk of CVDs and mean daily doses of antipsychotics (p value for non-linearity=0.008; p value for overall trend <0.001). The risk of CVDs increased rapidly with increase in mean daily doses, and the increase slowed down when the mean daily doses reached about 0.7 DDD (figure 3B).

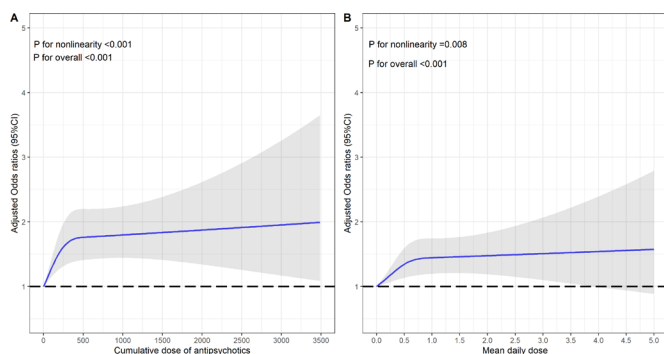


Figure 3 Cubic spline model of the association between dose of antipsychotics and risk of CVDs after adjusted: (A) cumulative dose of antipsychotics and (B) mean daily dose.

DISCUSSION

In the current study, we explored the associations between antipsychotics and incident CVDs using a large cohort of Chinese individuals with schizophrenia. We found that any antipsychotics use was associated with over 50% increased risk of any CVDs, with the association mainly driven by specific CVDs such as ischaemic heart diseases. The strengths of the associated risks also differed by specific types of antipsychotics. Medications such as haloperidol, risperidone and quetiapine are worth emphasised attention, especially in patients at higher risk for cerebrovascular diseases and ischaemic heart diseases. Moreover, we found a non-linear dose–response relationship between risk of CVDs and antipsychotics use, with a sharp increase in risk at low dosage levels, which then flattens out at higher cumulative levels.

Our results support a significant association between antipsychotic medication treatment and risk of CVDs after adjustment for potential confounders, including comorbidities, which is consistent with multiple previous studies.^{13 14} Additionally, we found that combination use of FGAs and SGAs presented even stronger associations. This may indicate an assertion of adverse effects on the incidence of CVDs from mixed use of antipsychotics.^{25 26} Most of the current treatment guidelines and protocols also recommend monotherapy to reduce potential side effects.²⁶ On the other hand, switching between different types of antipsychotics may happen to individuals with more severe schizophrenic symptoms, who might also suffer from poorer health conditions in general. When considering initiating or switching antipsychotics to individuals with schizophrenia, clinicians should be cautious with regard to the risk of CVDs.

In different outcomes of CVDs, we found that overall antipsychotics were mainly associated with ischaemic heart diseases. Specific drug analyses also reflect that ischaemic heart disease is associated with most antipsychotics. This suggests that

antipsychotic drugs may primarily affect the function of cardiac-related systems. Although overall antipsychotics were not associated with cerebrovascular disease in this study, some specific drugs, such as haloperidol, risperidone and quetiapine, still showed a higher risk of cerebrovascular disease. Therefore, there remains lack of evidence that clarifies whether and how antipsychotics affect specific cardiovascular adversities; however, individuals with schizophrenia at high risk of specific conditions such as ischaemic heart diseases should be carefully examined before initiating or tailoring therapies with antipsychotics.

Our research found that different antipsychotic drugs differ in their risk for CVDs. Specific medications such as haloperidol, aripiprazole, quetiapine, olanzapine, risperidone, sulpiride and chlorpromazine presented significantly higher risk of any CVDs. Among them, use of haloperidol, quetiapine and risperidone was associated with a high risks of common CVDs, including cerebrovascular diseases and ischaemic heart diseases. Previous studies have found that chlorpromazine, olanzapine, quetiapine, risperidone and oral haloperidol have moderate to high levels of metabolic risk, among which chlorpromazine and olanzapine caused a weight gain of >2kg; quetiapine, risperidone and oral haloperidol were associated with a weight gain of 1–2kg; and antipsychotics such as aripiprazole, perphenazine and ziprasidone were associated with a weight gain of <1kg or a weight loss with low metabolic risk.²⁷ Thus, differences in the metabolic side effects of antipsychotic drugs explain our results. However, some antipsychotics with high metabolic risk, especially clozapine, showed no association with CVDs in our results. In addition to population differences, drug dosage may account for clozapine's lower risk of CVDs. Clozapine can lead to agranulocytosis and neutropaenia, which may endanger patients' lives. The Chinese Guidelines for the Management of Schizophrenia clearly recommend that clozapine should be used with caution.²⁸ Clinicians should be more cautious when prescribing clozapine and should control its dosage for safety, which may reduce the risk of CVDs. Heterogeneity in terms of not only treatment effectiveness but also the potential risk for severe conditions such as CVDs should be included in the routine checklist for clinical use of antipsychotics.

We observed a non-linear dose–response pattern where the risk of CVDs increased by cumulative dosages and mean daily dose of antipsychotics. Similar results were reported by previous studies on the risk of acute myocardial infarction and atrial fibrillation.^{9–10} Lin *et al*⁹ showed that the risk of acute myocardial infarction significantly increased with cumulative dose of antipsychotics. In our study, the risk of CVDs increased in proportion to elevation in cumulative doses of antipsychotics, up to an inflection point of around 500 cDDD, where the slope of the relationship was attenuated, although we did not have enough power to specifically analyse acute myocardial infarction. In addition, the mean daily dose showed a dose–response pattern similar to that of the cumulative dose, with an inflection point at 0.7 DDD. Underlying mechanisms need further investigation, but the risks and benefits of initiation and continuation of antipsychotics should be thoroughly assessed in clinical practice.

Strengths and limitations

Key strengths of this study include the large sample size that was based on provincial longitudinal registers containing extensive individual-level data collected systematically and covering a population of over 100 million in China. We were able to investigate the risk of incident CVDs related to different types of antipsychotics and explored the associations regarding

substantially common CVDs. Given the comprehensive coverage of information in our data, we were able to adjust for important confounders, including lifestyle factors as well as physical and mental comorbidities. Our study also has several limitations. First, this study was based on retrospectively collected register-based data. Adherence to antipsychotics prescriptions may not be perfect, which could result in possible misclassification of exposures and assessment of doses. Patients' medication usage through other channels (such as private clinics) may not be recorded either. Thus, some non-users of antipsychotics may be misclassified, which may result in underestimation of the cardiovascular risk of antipsychotics. Moreover, covariates such as smoking and alcohol consumption were not assessed in specific quantities, and some potential confounding factors such as medication adherence were not available. Finally, although we adjusted for multiple groups of potential confounders, we lack longitudinal follow-up information in more detail. As a result, we could not further investigate concurrent exposure to multiple types of medications (polypharmacy). Nevertheless, our study findings add significant evidence to guide antipsychotics prescriptions among individuals with schizophrenia in terms of incident CVD risk.

CONCLUSIONS

Our data supports the association between elevated risk of incident CVDs and antipsychotics among individuals with schizophrenia. Clinicians should thoroughly assess the risk of CVDs when considering treatment with antipsychotics among individuals with schizophrenia and proactively address the potential CVD burden associated with antipsychotics.

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