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# Metabolic syndrome in chronic schizophrenia: Cross-sectional hospital assessment of prolonged risperidone exposure

**Yimin Wu[1], Jie Wu[1], Zuobin Deng[1] and Tao Xiao[2]***

[1]Department of Psychiatry, Ganzhou Third People's Hospital, 116 Qinglongshan Avenue, Ganzhou, Jiangxi 341000, China
[2]Department of Psychology, Ganzhou Third People's Hospital, 116 Qinglongshan Avenue, Ganzhou, Jiangxi 341000, China

**Abstract**: **Background**: Long-term use of antipsychotics like risperidone raises metabolic syndrome (MetS) risk, with evidence from Chinese populations being limited. **Objectives**: This study compared MetS prevalence and metabolic profiles between chronic schizophrenia patients on long-term risperidone versus olanzapine. **Methods**: In this cross-sectional study, 80 risperidone-treated patients were compared to 80 olanzapine-treated controls. MetS [IDF (The International Diabetes Federation) criteria], glucose/lipid metabolism and anthropometric measures were assessed. Statistical analyses included t-tests and $\chi^2$ tests. **Results**: The prevalence of MetS was significantly lower in the risperidone group (30.0%) compared to the olanzapine group (48.8%, $p = 0.015$). Risperidone patients showed better glycemic control and lipid profiles ($p < 0.05$), though BMI (body mass index), waist circumference and blood pressure remained elevated compared to olanzapine patients. **Conclusion**: Long-term risperidone therapy is associated with a lower MetS risk than olanzapine. Regular metabolic monitoring and adjunctive interventions are recommended for high-risk patients.

**Keywords**: Antipsychotic drugs; Chronic schizophrenia; Cross-sectional study; Metabolic syndrome; Prevalence; Risperidone

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## INTRODUCTION

Schizophrenia, a chronic and complex psychiatric disorder, affects approximately 0.3 – 0.7% of the global population (Leucht *et al*., 2025). Its core symptoms include positive symptoms (such as hallucinations and delusions), negative symptoms (such as apathy and social withdrawal), as well as cognitive impairments (Striebel 2025). Antipsychotic drugs are the main treatment for schizophrenia. Among them, SGAs (second-generation antipsychotic drugs) are widely used due to their lower extrapyramidal side effects (Feng *et al*., 2024). Risperidone, as one of the representative drugs of SGAs, has been available on the market since 1993. Due to its balanced control of positive and negative symptoms, it has become a first-line treatment option in clinical practice (Galderisi *et al*., 2021). However, with the accumulation of clinical application experience, the adverse effects of risperidone on metabolism have gradually attracted attention, especially the impact of long-term use on MetS (metabolic syndrome) in patients with chronic schizophrenia (Wu *et al*., 2025). Metabolic syndrome represents a cluster of conditions with insulin resistance at its pathophysiological core, characterized by central obesity, hyperglycemia, hypertension, hypertriglyceridemia and reduced HDL-C (high-density lipoprotein cholesterol) (Zheng *et al*., 2025). Clinically, it substantially elevates cardiovascular disease, cerebrovascular events and type 2 diabetes mellitus risk (Peng *et al*., 2023). Lifelong risperidone pharmacotherapy in chronic schizophrenia may potentiate metabolic dysregulation, amplifying pre-existing cardiovascular disease susceptibility in this high-risk population (Qiu *et al*., 2023; Yeh *et al*., 2025). Chronic schizophrenia necessitates long-term antipsychotic treatment. MetS - encompassing obesity, dyslipidemia, hypertension and insulin resistance - is alarmingly common in this population, significantly contributing to reduced life expectancy (10-20 years less than the general population) (Ronaldson *et al*., 2024).

Patients with schizophrenia exhibit an intrinsic predisposition to metabolic dysregulation, a risk not solely attributable to antipsychotic side effects (Meyer and Correll 2023). Research confirms that even treatment-naïve individuals experiencing first-episode psychosis demonstrate a markedly elevated prevalence of glucose and lipid metabolism abnormalities compared with the general population (Imre *et al*., 2025). Metabolomics studies have shown that in patients with schizophrenia, the levels of various metabolites (such as alanine, valine, glucose, lactic acid, lipoproteins) in their plasma and urine are abnormal, suggesting that there is an inherent disorder in amino acid metabolism, sugar metabolism and lipid metabolism (Liu *et al*., 2021). This underlying metabolic dysfunction may heighten vulnerability to the adverse metabolic effects of antipsychotic medications in individuals with schizophrenia. In addition, people with schizophrenia tend to have unhealthy lifestyles, such as poor diet, lack of exercise, high smoking rates, disturbed sleep patterns and frequent alcohol intake., (Fan *et al*., 2024). These factors further increase the risk of metabolic syndrome. Chronic hospitalized schizophrenia patients, due to limited mobility and decreased ability to control diet,

**Corresponding author:* e-mail: Xiaotao12122@hotmail.com

have particularly prominent metabolic problems (Pillinger *et al*., 2020). Studies have shown that the prevalence of metabolic syndrome among long-term hospitalized schizophrenia patients is as high as 32.5%, which is much higher than that of the general population (Tocco *et al*., 2021). This high incidence and prevalence rate indicates that special attention needs to be paid to the impact of long-term use of antipsychotic drugs (such as risperidone) on the metabolic health of patients with chronic schizophrenia.

Risperidone exerts its primary therapeutic effects through dopamine $D_2$ and serotonin 5-$HT_2$A receptor antagonism (Hutchinson *et al*., 2023). However, blockade of histamine $H_1$, 5-$HT_2$C and muscarinic $M_3$ receptors by this agent contributes to adverse metabolic outcomes, including weight gain, glucose intolerance and dyslipidemia (Elsevier 2023; Natalizio, Nigam and Rai 2025). Clinical data indicate that roughly half of schizophrenia patients initiating risperidone therapy exhibit ≥7% body weight increase during the initial 12-week treatment period (Ma *et al*., 2024). The increase in weight was most significant during the first three months after medication and persisted for at least six months. In terms of metabolic indicators, risperidone treatment was associated with several adverse changes: increased waist circumference, elevated TG (triglyceride) levels, and raised postprandial glucose. Additionally, a reduction in HDL-C was observed (Rikhari *et al*., 2022). It is worth noting that the metabolic side effects of risperidone show significant individual differences. Newly diagnosed patients who have not taken any antipsychotic drugs, patients with a family history of obesity or diabetes and those with a higher baseline body mass index or larger waist circumference are more likely to experience metabolic abnormalities after receiving risperidone treatment (Chen *et al*., 2023). These findings suggest that before prescribing medication, the metabolic risk factors of patients should be fully assessed and individualized treatment plans should be formulated.

Multiple established definitions exist for diagnosing metabolic syndrome, with widely implemented guidelines comprising those from The International Diabetes Federation (IDF), The National Cholesterol Education Program Adult Treatment Panel III guidelines (NCEP ATP III) and the Chinese Diabetes Society (CDS) (Nwankwo, Okamkpa and Danborno 2022). These criteria vary slightly in specific parameters, but all emphasize the multiple aggregations of central obesity and metabolic abnormalities. For patients with schizophrenia, the harm of metabolic syndrome is particularly severe because the cardiovascular disease mortality rate of schizophrenia patients is 2 to 3 times higher than that of the general population (Zhang *et al*., 2021). The existence of metabolic syndrome further exacerbates this risk (Feng *et al*., 2025). Furthermore, the clinical manifestations of metabolic syndrome in patients with schizophrenia have certain particularities. Due to impaired cognitive function and the absence of illness perception, patients often have less subjective perception and complaints of their own metabolic abnormalities, resulting in the concealed progression of the disease; on the other hand, metabolic abnormalities caused by antipsychotic drugs usually first manifest as weight gain and abdominal obesity and then abnormal indicators of sugar and lipid metabolism appear. This progressive development characteristic provides a time window for early intervention, but it also requires clinicians to actively monitor relevant indicators instead of waiting for patients to make complaints (DeJongh 2021).

While numerous investigations have elucidated associations between antipsychotic medications and metabolic syndrome, systematic analysis of risperidone's long-term metabolic consequences in chronic schizophrenia populations remains notably deficient. Existing research predominantly features modest sample sizes and brief observation windows, substantially limiting comprehensive evaluation of extended metabolic outcomes. For instance, a representative trial enrolled merely 29 risperidone-treated schizophrenia patients over a 16-week monitoring period (Birur *et al*., 2020). This short-term research design is unable to accurately reflect the real situation of chronic patients who need to take medication for life. Moreover, the existing studies have insufficient control over confounding factors. The metabolic status of patients with schizophrenia is influenced by various factors, including genetic background, lifestyle, comorbid conditions and concurrent medication use. Numerous investigations inadequately controlled for potential confounders, introducing bias toward either inflated or attenuated assessments of risperidone's intrinsic metabolic risks (Wu *et al*., 2023). The research methods also exhibit heterogeneity. Different studies adopt different diagnostic criteria for metabolic syndrome and the assessment indicators and time points vary, making it difficult to directly compare and integrate the research results. More importantly, there is a relative lack of research data for the Chinese population. Due to differences in genetic background, dietary habits and body composition characteristics, the research results from Western populations may not be fully applicable to Chinese patients.

The conclusions regarding the comparison of the metabolic risks of risperidone with other antipsychotic drugs vary. Some studies indicate that the metabolic risk of risperidone is lower than that of olanzapine and clozapine, but higher than that of aripiprazole and ziprasidone (Zhang *et al*., 2020). A recent retrospective cohort study comparing aripiprazole and risperidone showed that after 24 weeks of treatment, the patients in the aripiprazole group had significantly better weight and blood pressure levels than those in the risperidone group (Richards-Belle *et al*., 2025). These findings provide important references for clinical drug selection. For patients exhibiting pre-existing metabolic abnormalities, adjunct metformin therapy

effectively enhances glycolipid profiles when administered alongside risperidone. Animal studies modeling schizophrenia further reveal that concurrent metformin treatment sustains the therapeutic effects of risperidone and olanzapine on behavioral impairments, while simultaneously reducing metabolic disturbances associated with antipsychotic medication (Luo *et al*., 2020). These intervention strategies provide feasible solutions for the clinical management of metabolic side effects caused by risperidone.

Given the established research context, this investigation is designed to comprehensively assess the consequences of extended risperidone therapy (≥ 2 years) on metabolic syndrome incidence, prevalence and associated metabolic markers among hospitalized chronic schizophrenia patients, while also identifying contributing risk factors. The study will specifically: (1) Contrast metabolic syndrome prevalence rates between chronic schizophrenia patients undergoing long-term risperidone treatment and a demographically matched healthy control group; (2) Quantify longitudinal alterations in core metabolic parameters—including anthropometric measures (body mass index, waist circumference), hemodynamic values (blood pressure), glycemic indices (fasting plasma glucose) and lipid metabolism profiles—within the cohort receiving prolonged risperidone exposure; and ultimately provide evidence-based basis for the clinical formulation of reasonable use strategies and metabolic monitoring plans for risperidone.

## MATERIALS AND METHODS

### *Sample size calculation*

The sample size was calculated based on the data reported in the literature (Ko *et al*., 2013). The calculation is based on the formula for comparing rates of two independent samples: Let $\alpha = 0.05$ (two-tailed), with a confidence level of 95%. Using the formula for comparing rates of two independent samples, it is calculated that each group needs at least 70 cases. Factoring in anticipated participant attrition, the final sample size was established with 80 participants per group for both the risperidone and olanzapine cohorts. This calculation was performed employing G*Power software to guarantee adequate statistical power for detecting intergroup differences.

### *Research subjects and groupings*

This study adopted a cross-sectional research design, selecting patients with chronic schizophrenia who were treated in Ganzhou Third People's Hospital from January 2021 to January 2025. All patients met the ICD-11 (the International Classification of Diseases) diagnostic criteria for schizophrenia and were confirmed by two or more psychiatrists with the highest professional title (such as associate chief physicians) through a standardized diagnostic process. Initially, 243 patients with schizophrenia were screened. A total of 83 patients were excluded based on the following criteria: concomitant use of other psychotropic medications (n=71), use of metabolism-affecting drugs prior to enrollment (n=3), recent history of acute infection (n=4), diagnosis of other mental disorders (n=3), and presence of other serious physical diseases (n=2).The study cohort comprised 160 participants. Patients were stratified according to medication regimen, forming two distinct groups: a cohort receiving prolonged risperidone monotherapy (n=80) and an olanzapine-treated cohort (n=80). All study subjects came from the same region and had similar socioeconomic backgrounds and dietary habits. (Fig. 1).

### *Inclusion and exclusion criteria*

*Inclusion criteria* (Nickl-Jockschat *et al*., 2025): (1) It meets the diagnostic criteria for schizophrenia as stipulated in the 11th Edition of ICD-11 and is independently diagnosed and confirmed by two psychiatrists with the title of associate chief physician or above; (2) The age is between 18 and 65 years old; (3) The patient has been using risperidone monotherapy for ≥ 2 years continuously; (4) The dosage is stable (4 - 6mg/day) for ≥ 6 months; (5) Participants exhibited a total score of ≥ 60 on the PANSS (Positive and Negative Syndrome Scale); (6) The patient is able to cooperate and complete all examinations.

*Exclusion criteria* (Luo *et al*., 2020): (1) Comorbid with severe physical diseases (Confirmed cases of diabetes, Cushing's syndrome and polycystic ovary syndrome, liver and kidney dysfunction, thyroid dysfunction, malignant tumors, severe cardiovascular diseases); (2) Pregnant or lactating women; (3) Using drugs that may affect metabolism within 3 months before enrollment (such as glucocorticoids, hypoglycemic drugs, lipid-regulating drugs, diuretics.); (4) Having a history of severe adverse drug reactions; (5) Comorbidity with other psychiatric disorders, including depression, bipolar disorder and substance dependence; (6) Having a history of acute infection or trauma within the last 3 months. The control cohort shared identical eligibility criteria with the patient group, differing only by not requiring a diagnosis of schizophrenia. Written informed consent was obtained from all participants and the study protocol received approval from the hospital's ethics committee.

### *Detection indicators*

*Key indicator: Incidence/Prevalence of metabolic syndrome*

*Secondary indicators*

(1) Physical examination measurement indicators: Height, weight, waist circumference, pulse, blood pressure (systolic and diastolic), BMI (body mass index), WHR (waist-to-hip ratio);

(2) Glycemic metabolism indicators: FBG (fasting blood glucose), FINS (fasting insulin), HbA1c (glycosylated hemoglobin), HOMA-IR (insulin resistance index);

(3) Lipid metabolism indicators: TC (total cholesterol), TG, HDL-C, LDL-C (low-density lipoprotein cholesterol).

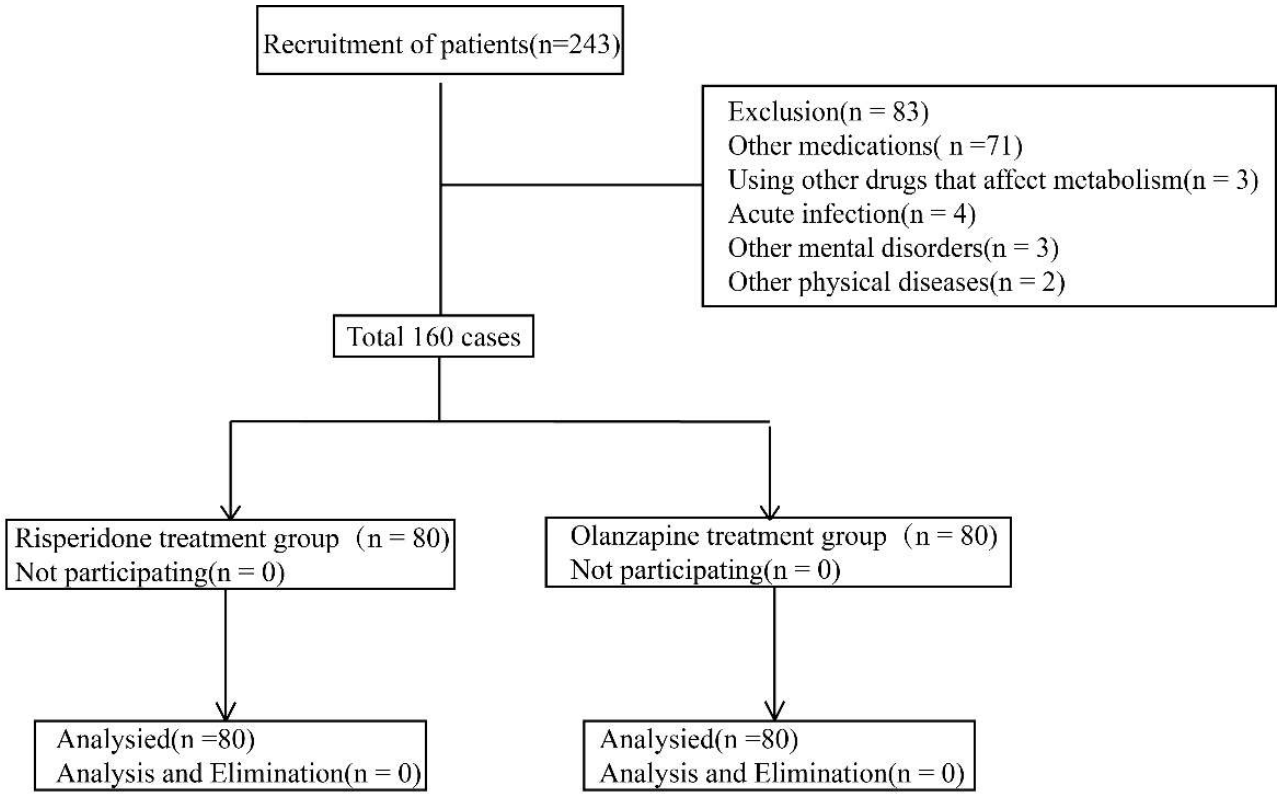


**Fig. 1**: Flowchart

(Flowchart explanation: In this cross-sectional study, 243 sluggishly progressing schizophrenia patients were divided into the risperidone monotherapy group, combination therapy group and other antipsychotic groups. The prevalence rate of metabolic syndrome and the levels of various metabolic indices were comprehensively evaluated by collecting the clinical data and laboratory test data of the patients. Using multivariate statistical analysis, the metabolic characteristics of different groups were compared and the independent risk factors of metabolic syndrome were discussed.)

***Testing method***

All tests were conducted using standardized methods.

(1) Anthropometric assessments were performed by uniformly trained nursing staff adhering to standardized protocols. Stature was determined to the nearest 0.1 cm using a wall-mounted stadiometer (Mitutoyo 570-314). Body mass was recorded with a calibrated electronic balance (precision: 0.1 kg). Waist circumference measurements, taken at the umbilical level following normal expiration and hip circumference assessments, conducted at the maximal gluteal protuberance, employed a non-elastic tape measure (accuracy: 0.1 cm). Seated blood pressure was ascertained after a 15-minute rest period using a mercury column sphygmomanometer, with reported values representing the mean of three consecutive measurements.

(2) Biochemical indicators: Fasting venous blood samples were obtained during morning hours. Biochemical analysis was performed using an automated Hitachi 7600 analyzer. Laboratory quality assurance protocols were strictly followed throughout the testing process. Inflammatory markers and oxidative stress parameters were quantified using ELISA (enzyme-linked immunosorbent assay) methodology. high-sensitivity C-reactive protein (HS-CRP, CSB-E086), interleukin-6 (IL-6, PI330), tumor necrosis factor-alpha (TNF-α, EK182) and superoxide dismutase (SOD, SP11149), intra-and inter-assay coefficients of variation were all < 10%. Insulin detection was performed using a chemiluminescence method and all operations were carried out in strict accordance with the reagent instructions and laboratory standard operating procedures.

(3) Diagnosis of metabolic syndrome: The double criteria of the International IDF and the CDS were adopted.

***Statistical analysis***

Statistical analyses were performed utilizing SPSS version 25.0. For quantitative variables, a preliminary assessment included evaluating normal distribution with the Shapiro-Wilk test and examining variance homogeneity via Levene's test. Among the baseline information, age, weight, BMI, TG, TC, LDL-C, Hb, HbA1c, 2hPG, HOMA-IR and the indicators related to glycolipid metabolism that met normal distribution were expressed as mean ± standard deviation ($\bar{x}\pm s$ ) and group comparisons were analyzed employing the independent samples t-test. For non-normally distributed variables, data are presented as median (interquartile range), whereas between-group differences were assessed via the Mann-Whitney U test.

Categorical variables, including smoking history, gender, presenting complaint and metabolic syndrome prevalence, were summarized as frequencies with corresponding percentages. Intergroup analyses for these parameters employed either Pearson's chi-square test or Fisher's exact test, with the latter applied when expected cell counts fell below five. Continuous measures between cohorts were evaluated using independent samples t-tests. Statistical significance was defined as a two-sided $p$ -$p$-value < 0.05 for all inferential analyses.

***Ethical statement***

All research procedures strictly adhere to the ethical guidelines of the Helsinki Declaration. Before the study began, detailed explanations of the study's purpose, process, potential risks, and benefits were provided to all potential participants (or their legal guardians) as well as healthy volunteers. It was ensured that participants understood they had the right to withdraw from the study at any stage unconditionally and that this would not affect their entitlement to medical services. Written informed consent was obtained from each participant. For patients with chronic schizophrenia, additional informed consent was obtained from their legal guardians, considering that their condition might affect their capacity to provide fully informed consent.To ensure the privacy of the participants, all the personal identification information collected has been replaced with anonymous codes before the data analysis and the data has been encrypted and stored throughout the entire research process.

## RESULTS

***Demographic part***

In this study, 160 patients with sluggishly progressing schizophrenia were divided into the risperidone group and the olanzapine group (80 cases each). There was no significant difference between the two groups in age (median age 33 years), gender (male accounted for about 55%) and proportion of high school education (about 54%) ($p > 0.75$), as shown in Table 1. No statistically meaningful difference was observed, indicating that there were no systematic errors in the baseline information of the patients and that the data were comparable.

***The prevalence of MetS in the two groups of patients***

The results (Table 2) show that according to the ATP III standards, both TC > 5.2 mmol/L and TG > 1.7 mmol/L are diagnostic criteria for metabolic syndrome. The probability of MetS occurrence in the risperidone treatment group was lower than that in the olanzapine treatment group and there was a statistically significant difference ($p = 0.015$).

***The physical examination test indicators of the two groups of patients***

Analysis of anthropometric measures revealed no significant differences in height, weight, or pulse rate between the two treatment groups. However, key indicators of central obesity—waist circumference, waist-to-hip ratio and BMI—were all significantly lower in the risperidone group compared to the olanzapine group (all $p < 0.05$). as shown in Tables 3, 4 and Fig. 2.

***Comparison of two groups of glucose metabolism indicators***

In terms of glucose metabolism indicators, the risperidone group showed a trend of being superior to the olanzapine group overall. As shown in Table 5 and Fig. 3, the FBG, HbA1c, FINS levels and HOMA-IR index of patients in the risperidone group were significantly lower than those in the olanzapine group (all comparisons $p < 0.01$), suggesting that patients treated with risperidone had better blood glucose control and insulin sensitivity.

***Comparison of lipid metabolism indicators between the two groups***

Compared with the olanzapine group, the risperidone group showed more favorable characteristics in lipid profile. Specifically, patients in the risperidone group had significantly lower serum levels of TC, TG and LDL-C, while HDL-C levels were significantly higher ($p < 0.05$ for all comparisons, Table 6 and Fig. 4).

***Multivariate logistic regression analysis***

After adjusting for age, sex, family history of diabetes and waist circumference before treatment, binary logistic regression analysis showed that the treatment group was an independent predictor of the development of metabolic syndrome ($p < 0.05$). Patients in the olanzapine group had a significantly higher risk of developing metabolic syndrome compared with risperidone, with an odds ratio of 2.220 [95% CI: (1.160-4.246)], as shown in Table 7.

## DISCUSSION

Although risperidone and olanzapine are both non-traditional first-line antipsychotic drugs, there are differences in their long-term metabolic risk profiles and these have not been fully clarified. Most existing comparative studies are short-term or involve combined medication. For the Chinese population with chronic schizophrenia, in a long-term monotherapy mode, there is still a lack of cross-sectional evidence for systematically comparing the effects of the two on metabolic syndrome and its key components (such as insulin resistance and atherosclerotic lipid profile). This evidence gap leaves clinicians lacking precise metabolic safety data based on specific populations when formulating treatment plans for chronic patients who require long-term medication. This study aims to fill this gap by conducting a cross-sectional survey to directly compare the effects of long-term use of risperidone and olanzapine monotherapy on the prevalence of metabolic syndrome and related metabolic indicators in Chinese patients with chronic schizophrenia.

**Table 1**: Baseline information comparison ($\bar{x}$±s)

| Parameters | | Group A(n=80) | Group B(n=80) | Test | z/t/$x^2$ | p |
|---|---|---|---|---|---|---|
| Age *[ median (quartile, quartile)]* | | 33 (27.00, 44.50) | 33 (27.00,45.75) | Mann-Whitney U test | -0.311 | 0.756 |
| Gender, *n* (%) | *Male* | 45 (56.25) | 43 (53.75) | Chi-squared | 0.101 | 0.751 |
| | *Female* | 35 (43.75) | 37 (46.25) | | | |
| Educational attainment, *n* (%) | *High school and below* | 38 (47.50) | 36 (45.00) | Chi-squared | 0.101 | 0.751 |
| | *High school level or above* | 42 (52.50) | 44 (55.00) | | | |
| Smoking history, *n (%)* | *Yes* | 35 (43.75) | 34 (42.50) | Chi-squared | 0.025 | 0.873 |
| | *No* | 45 (56.25) | 35 (57.50) | | | |
| Family history of diabetes, *n* (%) | *Yes* | 42 (52.50) | 44 (55.00) | Chi-squared | 0.101 | 0.751 |
| | *No* | 38 (47.50) | 36 (45.00) | | | |
| Course of the disease (year) | | 8 (3,13) | 7 (3,14) | Mann-Whitney U test | -0.029 | 0.977 |

Note: Group A is the risperidone treatment group and Group B is the olanzapine treatment group. For continuous variables that do not conform to a normal distribution, the median (dichotomous, quartile) form is used for presentation. Comparisons between groups were performed by the Mann-Whitney U test, and descriptive statistics and test statistics were reported in the above format with Z-values and p-values.

**Table 2**: Comparison of occurrence situations between the two groups of MetS [*n*(%)]

| Parameters | Group A | Group B | $x^2$ | *p* |
|---|---|---|---|---|
| Mets Occurrence, *n* (%) | 24 (30.00) | 39 (48.75) | 5.891 | 0.015 |

Note: Group A is the risperidone treatment group and Group B is the olanzapine treatment group.

**Table 3**: Evaluating physiological measures between study groups (Mann-Whitney U test, $\bar{x}$±s)

| Parameters | | Group A(n=80) | Group B(n=80) | Test | Z | p |
|---|---|---|---|---|---|---|
| Pulse | | 85.50 (80.00, 88.00) | 86.00 (80.25, 91.00) | Chi-squared | -1.332 | 0.183 |
| Blood pressure (mmHg) | *Systolic blood pressure* | 118.00 (112.00,126.75) | 122.91 ± 10.74 | Mann-Whitney U test | -2.585 | 0.010 |
| | *Diastolic blood pressure* | 78.00 (72.25,84.50) | 80.75 ± 8.16 | Mann-Whitney U test | -2.010 | 0.044 |
| Height(m) | | 1.68 (1.61， 1.74) | 1.67 (1.61, 1.72) | Chi-squared | -0.998 | 0.318 |
| Waist circumference(cm) | | 93.85±11.02 | 99.69 (91.17, 104.74) | Mann-Whitney U test | -2.143 | 0.032 |

Note: Group A is the risperidone treatment group and Group B is the olanzapine treatment group. For continuous variables that do not conform to a normal distribution, the median (dichotomous, quartile) form is used for presentation. Comparisons between groups were performed by Mann-Whitney U test, and descriptive statistics and test statistics were reported in the above format with Z-values and p-values.

**Table 4**: Evaluating physiological measures between study groups (T test, $\bar{x}$±s)

| Parameters | Group A(n=80) | Group B(n=80) | Test | 95% CI | | Standard error | | t | *p* |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Lower | upper | Group A | Group B | | |
| Weight (kg) | 71.20 ± 15.15 | 72.86 ± 14.07 | t test | -6.223 | 2.906 | -6.224 | 2.906 | -0.718 | 0.474 |
| BMI (kg/m$^2$) | 25.25 ± 5.08 | 26.82 ± 4.80 | t test | -3.122 | -0.04 | -3.122 | -0.038 | -2.024 | 0.045 |
| WHR (ratio) | 0.92 ± 0.04 | 0.98 ± 0.03 | t test | -0.074 | -0.049 | -0.074 | -0.049 | -9.948 | <.001 |

Note: Group A is the risperidone treatment group, and Group B is the olanzapine treatment group.

**Table 5**: Comparison of two groups of glucose metabolism indicators ($\bar{x}$±s)

| Parameters | Group A (n=80) | Group B (n=80) | Test | 95% CI | | Standard error | | t | *p* |
|---|---|---|---|---|---|---|---|---|---|
| | | | | *Lower* | *Upper* | *Group A* | *Group B* | | |
| FPG (mg/dl) | 106.15 ± 9.89 | 110.25 ± 9.26 | t test | -7.087 | -1.103 | -2.704 | 1.105 | 1.035 | 0.008 |
| FINS (pmol/L) | 8.89 ± 1.52 | 9.53 ± 0.68 | t test | -1.008 | -0.271 | -3.431 | 0.170 | 0.075 | 0.001 |
| HbAlc (%) | 5.46 ± 1.24 | 5.90 ± 0.51 | t test | -0.727 | -0.133 | -2.863 | 0.139 | 0.056 | 0.005 |

Note: Group A is the risperidone treatment group and Group B is the olanzapine treatment group.

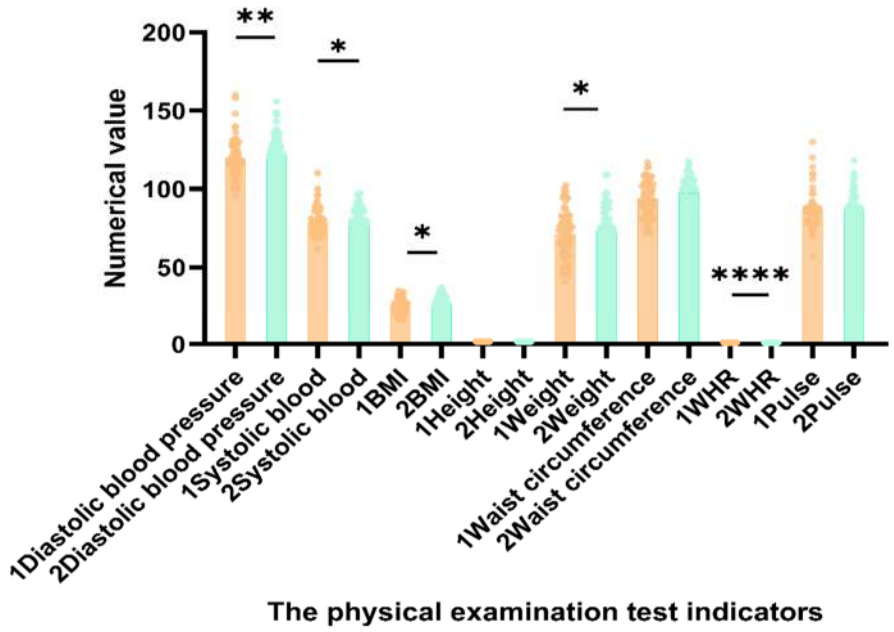


**Fig. 2**: Physical examination indicators
Note: 1 is the risperidone treatment group; 2 is the olanzapine treatment group. Data are presented as mean ± SEM. * $p < 0.05$, * * $p < 0.01$, * * * $p < 0.001$, * * * * $p < 0.0001$ compared with the control group.

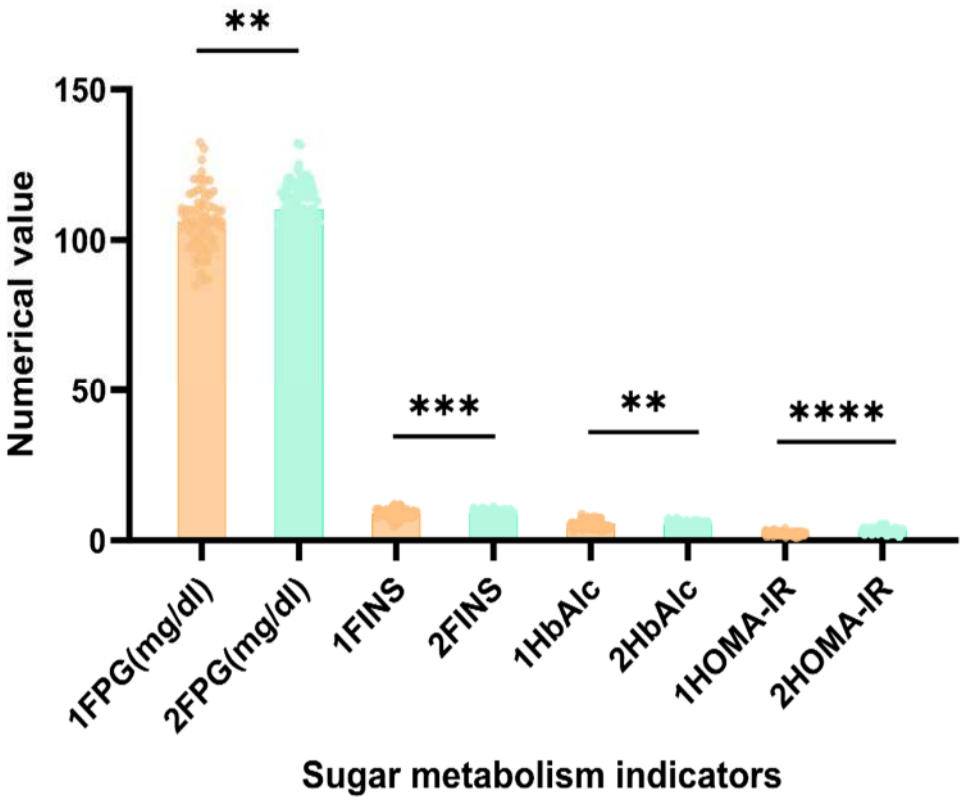


**Fig. 3**: Sugar metabolism indicators
Note: 1 is the risperidone treatment group; 2 is the olanzapine treatment group. Data are presented as mean ± SEM. * $p < 0.05$, * * $p < 0.01$, * * * $p < 0.001$, * * * * $p < 0.0001$ compared with the control group.

**Table 6**: Intergroup analysis of lipid profile parameters ($\bar{x}$±s)

| Parameters | Group A (n=80) | Group B (n=80) | Test | 95% CI | | Standard error | | t | *p* |
|---|---|---|---|---|---|---|---|---|---|
| | | | | *Lower* | *Upper* | *Group A* | *Group B* | | |
| TC (mmol/L) | 5.06 ± 1.76 | 5.57 ± 1.20 | t test | -0.971 | -0.029 | -2.099 | 0.197 | 0.133 | 0.037 |
| TG (mmol/L) | 2.18 ± 1.12 | 2.52 ± 1.02 | t test | -0.675 | -0.005 | -2.009 | 0.125 | 0.115 | 0.046 |
| HDL-C (mmol/L) | 0.65 ± 0.26 | 0.54 ± 0.31 | t test | 0.012 | 0.188 | 2.252 | 0.029 | 0.034 | 0.026 |
| LDL-C (mmol/L) | 2.65 ± 1.04 | 2.98 ± 0.92 | t test | -0.638 | -0.022 | -2.116 | 0.117 | 0.103 | 0.036 |

Note: TC stands for Total cholesterol; TG represents Triglyceride; HDL-C is High density lipoprotein cholesterol; LDL-C is Low density lipoprotein cholesterol.

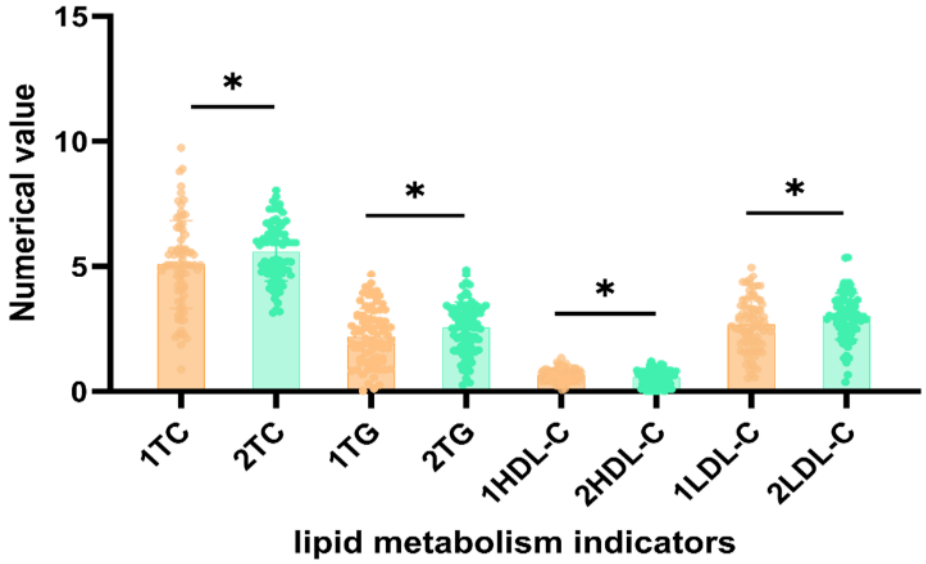


**Fig. 4**: Lipid metabolism indicators

Note: 1 is the risperidone treatment group; 2 is the olanzapine treatment group. * $p < 0.05$, * * $p < 0.01$, * * * $p < 0.001$, * * * * $p < 0.0001$ compared with the control group.

**Table 7**: Logistic regression analysis

| Parameters | B | SE | Wald | df | *p* -value | Exp (B) | The 95% CI of Exp (B) |
|---|---|---|---|---|---|---|---|
| FPG (mg/dl) | 0.008 | 0.017 | 0.229 | 1 | 0.632 | 1.008 | 0.976-1.041 |
| FINS (pmol/L) | -0.032 | 0.133 | 0.057 | 1 | 0.812 | 0.969 | 0.747-1.257 |
| HbAlc (%) | 0.185 | 0.169 | 1.190 | 1 | 0.275 | 1.203 | 0.863-1.677 |
| HOMA-IR (index) | 0.294 | 0.177 | 2.777 | 1 | 0.096 | 1.342 | 0.949-1.897 |
| TC (mmol/L) | 0.044 | 0.107 | 0.171 | 1 | 0.680 | 1.045 | 0.848-1.288 |
| TG (mmol/L) | 0.279 | 0.154 | 3.278 | 1 | 0.070 | 1.322 | 0.977-1.789 |
| HDL-C (mmol/L) | 0.625 | 0.576 | 1.176 | 1 | 0.278 | 1.869 | 0.604-5.784 |
| LDL-C (mmol/L) | 0.296 | 0.168 | 3.094 | 1 | 0.079 | 1.344 | 0.967-1.870 |
| BMI ($kg/m^2$) | 0.020 | 0.033 | 0.380 | 1 | 0.538 | 1.020 | 0.957-1.088 |
| Waist circumference (cm) | 0.027 | 0.016 | 2.938 | 1 | 0.087 | 1.027 | 0.996-1.059 |
| Groups | 0.797 | 0.331 | 5.802 | 1 | 0.016 | 2.220 | 1.160-4.246 |

In this cross-sectional study, it was found that in sluggishly progressing schizophrenia patients, long-term risperidone use was associated with a lower incidence of metabolic syndrome, a better glycemic and lipid profile and less abdominal obesity than olanzapine. Multivariate analysis further confirmed that the choice of treatment was an independent factor affecting Mets risk. From the perspective of pathophysiological mechanisms, the metabolic abnormalities induced by antipsychotic drugs involve multiple receptor interactions and complex regulation of signaling pathways (Balashova *et al*., 2023; Chang *et al*., 2021). Risperidone, as a dual antagonist of dopamine D2 receptors and serotonin 5-HT2A receptors, has its impact on metabolism mainly achieved by interfering with the hypothalamic appetite regulation center (Li *et al*., 2021). Specifically, the moderate

antagonistic effect of risperidone on the histamine $H_1$ receptor may lead to increased appetite and reduced energy expenditure, while the blocking of the 5-HT2C receptor may further exacerbate this effect (Wan *et al*., 2020). Furthermore, risperidone may also affect insulin signal transduction and adipocyte differentiation, leading to peripheral insulin resistance and lipid metabolism disorders (Biswas *et al*., 2023). In a mouse experiment conducted, it was found that risperidone treatment for 56 days impaired glucose homeostasis by reducing Akt phosphorylation and GLUT4 expression (indicative of disrupted insulin signaling) (Tsai *et al*., 2021). It also caused an increase in visceral fat, hypertrophy of adipocytes and hypertriglyceridemia - suggesting impaired insulin action in peripheral tissues and lipid imbalance. It is worth noting that the receptor binding profiles of different SGAs vary significantly. In a study of mice, olanzapine antagonism of 5-$HT_2$C (5-Hydroxytryptamine Receptor 2C) was found to reduce interaction with $GHSR_1$a (growth hormone-releasing peptide receptor), increase production of the orexigenic NPY (neuropeptide Y), and promote hyperphagia and weight gain (Chen *et al*., 2020). In a study (de Bartolomeis *et al*., 2023), it was pointed out that the affinity of the $H_1$ receptor is exponentially correlated with the maximum weight gain of antipsychotic drugs - olanzapine and clozapine, which have high $H_1$ binding, cause the greatest weight gain, while ziprasidone and aripiprazole, which have the lowest $H_1$ affinity, show a lower metabolic risk. This explains why the metabolic effects of olanzapine (which has stronger H1 and 5-$HT_2$C antagonistic effects) are more prominent. However, regarding the cumulative effects of long-term use of risperidone (such as over 2 years) on metabolism, the existing research data are still insufficient, especially lacking direct comparative studies with olanzapine. This investigation addresses current knowledge gaps through rigorous matching of demographic/clinical covariates and implementation of a multidimensional metabolic profiling protocol.

In terms of physical indicators, the data from this study show that patients who have used olanzapine for a long time exhibit more significant weight gain and central obesity. The BMI of the olanzapine group reached 26.82 ± 4.80 kg/m², significantly higher than that of the risperidone group, which was 25.25 ± 5.08 kg/m² ($p = 0.022$). Elevated BMI (>25 kg/m²) is an established independent predictor of cardiovascular disease, underscoring the clinical relevance of these intergroup differences (Yao *et al*., 2025; Zabeen *et al*., 2023). The intergroup differences in waist circumference and WHR were also significant. The values for the olanzapine group were 93.85 ± 11.02 cm and 0.98 ± 0.03, respectively, while those for the risperidone group were 99.69 (91.17, 104.74) cm and 0.92 ± 0.06 (all $p < 0.05$). The results corroborated prior evidence in which weight gain with olanzapine therapy was found to be significantly more pronounced than with risperidone (Δ = 2.4–2.6 kg) (Zhou *et al*., 2023). It is worth noting that although the average BMI of the risperidone group was lower than that of the olanzapine group in this study, it was still higher than the normal range for healthy people (18.5 - 23.9 kg/m²), suggesting that long-term risperidone treatment may still lead to clinically significant weight gain. In terms of blood pressure indicators, the SBP (Systolic blood pressure) and DBP (Diastolic blood pressure) of the risperidone group were 118.00 (112.00, 126.75) and 78.00 (72.25, 84.50) respectively, slightly lower than those of the olanzapine group, which were 122.91 ± 10.74 mmHg and 80.75 ± 8.16 mmHg, but the difference was statistically significant ($p < 0.05$). The cardiovascular side effects of risperidone treatment were less than those of olanzapine. The comparative analysis of sugar metabolism indicators revealed a more complex drug-specific effect. The olanzapine group significantly performed worse than the risperidone group in terms of FPG, FINS and HOMA-IR (all $p < 0.01$). Specifically, the FPG of the olanzapine group was 110.25 ± 9.26 mg/dl, which had reached the diagnostic criteria for prediabetes WHO standard: 100 - 125 mg/dL (American Diabetes Association Professional Practice Committee 2022), while the FPG of the risperidone group was 106.15 ± 9.89, although lower than that of the olanzapine treatment group, it was still higher than the WHO standard (WHO, 1980). More critically, the insulin resistance metric demonstrates particular clinical relevance. The olanzapine cohort demonstrated significantly elevated HOMA-IR levels (3.46 ± 0.85) relative to risperidone-treated subjects (2.27 ± 0.54; $p < 0.01$) and had exceeded the commonly used cut-off value for insulin resistance (2.5). This finding is highly consistent with the drug's mechanism of action, as the strong antagonistic effect of olanzapine on the muscarinic M3 receptor can directly affect the function of pancreatic β cells and its interference with adipocytokines is more significant (Grajales *et al*., 2022). HbA1c measurements corroborate these findings, with olanzapine-treated subjects exhibiting significantly elevated levels (5.90 ± 0.51%) compared to risperidone recipients (5.46 ± 1.24%; $p < 0.05$). Given HbA1c's role as a biomarker of chronic glycemic control, these results indicate olanzapine may induce more sustained and clinically significant glucose dysregulation. It is worth noting that although the HbA1c level in the risperidone group was within the normal range (< 6.5%), 38.8% of the patients were in the pre-diabetic range (5.7 - 6.4%), indicating that even "moderate-risk" SGAs may still lead to clinically significant glucose metabolism abnormalities when used for a long term.

The inter-group differences in lipid metabolism indicators were also significant and had clinical significance. The TC and TG levels in the olanzapine group were 5.57 ± 1.20 mmol/L and 2.52 ± 1.02 mmol/L, respectively, which were significantly higher than those in the risperidone group (5.06 ± 1.76 mmol/L and 2.18 ± 1.12 mmol/L, $p$ values were 0.037 and 0.046, respectively). The extent of this difference was sufficient to affect cardiovascular risk

assessment, as according to the ATP III standard, TC > 5.2 mmol/L and TG > 1.7 mmol/L are both diagnostic criteria for metabolic syndrome. The inter-group difference in HDL-C was also significant, with the olanzapine group being 0.54 ± 0.31 mmol/L, which was lower than the 0.65 ± 0.26 mmol/L in the risperidone group ($p < 0.05$). This finding is particularly important because for every 0.1 mmol/L increase in HDL-C, the risk of vascular events decreases by approximately 5% (Georgoulis *et al*., 2022). There were also inter-group differences in low-density LDL-C (Olanzapine group: 2.98 ± 0.92 mmol/L vs. Risperidone group: 2.65 ± 1.04 mmol/L, $p < 0.05$). From a mechanistic perspective, olanzapine may increase the expression of SREBPs (Sterol regulatory element-binding protein ), promoting liver lipid synthesis, while inhibiting the activity of LPL ( Lipoprotein lipase) and delaying the clearance of peripheral TG (Chen *et al*., 2022; Pozzi *et al*., 2024). Risperidone has a relatively mild effect on these pathways, but long-term use can still lead to a progressive deterioration of the lipid profile (Pozzi *et al*.,, 2024).

However, for newly diagnosed patients, especially those with high-risk factors for metabolic syndrome (such as obesity, family history of diabetes), the initial drug selection should be more inclined towards SGA drugs with lower metabolic risks (such as aripiprazole or risperidone). For patients who have already exhibited metabolic abnormalities, the following intervention strategies can be considered: Firstly, strengthen lifestyle intervention, including personalized dietary plans and regular exercise; Secondly, consider the use of metabolic-regulating drugs, such as metformin, which has been proven to significantly improve insulin resistance caused by SGA drugs (Varalda *et al*., 2024). Finally, under the condition of stable symptoms, it is advisable to gradually reduce the dose of risperidone or partially replace it with metabolically neutral drugs. It is worth noting that this study found that although the metabolic indicators of the risperidone group were better than those of the olanzapine group, a considerable proportion of patients still showed clinically significant abnormalities. This suggests that even for "moderate-risk" SGAs, long-term use still requires close monitoring of metabolic parameters.

This study explores the risk factors influencing the occurrence of metabolic syndrome in long-term risperidone users, such as the duration of medication, cumulative dosage and baseline characteristics. By using a relatively large sample size and long-term medication standards, it can more accurately assess the long-term metabolic effects of risperidone; Strictly matching the control group and adopting a unified diagnostic standard can improve the comparability and reliability of the results; Comprehensive analysis of multiple potential risk factors can provide a reference for identifying high-risk patients; All data are from the Chinese population and the results have direct guiding value for clinical practice in China.

From the perspective of clinical practice, this study has enhanced psychiatrists' understanding of the long-term metabolic risks of risperidone, promoting the individualized selection of treatment plans; It has also provided targeted metabolic monitoring plans for patients using risperidone for a long time, enabling early detection and intervention; It has also offered reference for patients with high metabolic risks to switch medications (such as switching to aripiprazole with less metabolic impact) or adopt combined intervention strategies (such as combined treatment with metformin). With the popularization of the "whole-course management" concept in the treatment of schizophrenia, maintaining the physical health of patients while controlling their mental symptoms has become a major challenge for clinical practice. This research contributes critical data to inform the risk-benefit assessment of antipsychotic therapy, ultimately enhancing longitudinal outcomes and functional recovery in schizophrenia. Future research can further explore the molecular mechanisms of metabolic abnormalities caused by risperidone and develop more effective prevention and intervention measures, providing more scientific evidence for the comprehensive rehabilitation of schizophrenia patients.

The limitations of this study need to be taken into account when interpreting the results. Firstly, the cross-sectional design cannot determine causal relationships; differences in metabolic indicators may have existed before medication. Secondly, the potential confounding factors, such as patients' dietary patterns, exercise habits and family history, were not systematically evaluated. Lastly, all patients came from the same medical center, which may affect the generalizability of the results. Future studies should adopt a prospective design, combined with genomic technologies, to identify susceptible populations with metabolic abnormalities and explore individualized intervention strategies.

## CONCLUSION

In conclusion, although patients with chronic schizophrenia who have been using risperidone for a long time have significantly lower metabolic risks compared to those using olanzapine, they may still experience clinically significant weight gain, impaired glucose tolerance and abnormal blood lipids. Clinicians should strive to find a balance between therapeutic efficacy and metabolic safety and optimize the long-term prognosis of patients through regular monitoring and timely intervention.

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***Authors' contributions***
Yimin Wu and Tao Xiao: Developed and planned the study, performed experiments and interpreted results. Edited and refined the manuscript with a focus on critical intellectual

contributions; Jie Wu and Zuobin Deng: Participated in collecting, assessing and interpreting the data. Made significant contributions to data interpretation and manuscript preparation.

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The data that support the findings of this study are available from the corresponding author upon reasonable request.

***Ethical approval***
This study was approved by the Ethics Committee of Ganzhou Third People's Hospital (Approval No: gzsyy2024079). This study was performed in adherence with the STROBE guidelines. See supplementary file for the STROBE checklist.

***Conflict of interest***
The authors declare that they have no conflicts of interest.

***Consent to participate***
A signed informed consent form was secured from every participant.

***Supplementary data***
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