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Long-Term Metabolic Risk Associated with Clozapine in People with Schizophrenia: A Population-based Study in Hong Kong

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Abstract

Clozapine is the only pharmacological treatment effective for treatment-resistant schizophrenia, but concerns about cardiometabolic adverse effects may discourage its use. Population-level, long-term data comparing major adverse cardiovascular events (MACE) and metabolic disease progression between clozapine users (ClozUs) and non-clozapine antipsychotic users (Non-ClozUs) remain scarce. We conducted a retrospective cohort study using Hong Kong Hospital Authority electronic health records (2003–2019; follow-up through 2023), comparing incident ClozUs with Non-ClozUs matched 1:3 by age, sex, and illness duration. Primary outcomes were new-onset MACE and metabolic diseases (diabetes, hypertension, dyslipidemia, and obesity), assessed using adjusted Cox proportional-hazards models. Secondary outcomes included progression from a single metabolic condition to cardiometabolic multimorbidity or MACE; sensitivity analyses compared clozapine with olanzapine. Among 19,132 patients (mean [SD] age, 39.42 [11.85] years; 49.72% female; mean follow-up, 12.78 years), 4,783 ClozUs had risks of MACE, diabetes, and dyslipidemia comparable to Non-ClozUs, but lower risks of hypertension (adjusted hazard ratio [aHR], 0.76; 95% confidence interval [CI], 0.68–0.84) and obesity (aHR, 0.56; 95% CI, 0.46–0.69). ClozUs also had a lower rate of progression to cardiometabolic multimorbidity or MACE (32.18% vs. 41.31%; P < 0.001). Sensitivity analyses showed lower risks of hypertension, dyslipidemia, and obesity with clozapine than with olanzapine. Older age, male sex, depression, and substance use were associated with metabolic conditions among ClozUs. These findings indicate that metabolic concerns alone should not preclude clozapine treatment and support structured, individualized cardiometabolic monitoring for people receiving antipsychotics.

Introduction

Patients with schizophrenia have a two- to threefold higher mortality rate than the general population[1–4], largely driven by cardiovascular disease. Diabetes mellitus, hypertension, hyperlipidaemia and obesity are more prevalent among patients with schizophrenia than in the general population[5–7]. A meta-analysis of 92 randomized controlled trials (RCTs) revealed that both first- and second-generation antipsychotics are associated with adverse effects on metabolic risk, though no significant direct effect on major cardiovascular events such as myocardial infarction and stroke was found[8]. Different antipsychotics are likely not metabolically equivalent, but a comprehensive comparison of the metabolic profiles of individual drugs was limited[8].

Clozapine is the drug of choice for treatment-resistant schizophrenia (TRS), demonstrating superior efficacy in symptom remission[9], and reducing mortality[10, 11], suicidality, aggressive behaviours and hospitalization[12–14]. However, its significant propensity for metabolic dysregulation elevates cardiovascular risk, posing a barrier to clozapine initiation. Accurate data on the degree of metabolic risk associated with clozapine are important to aid clinicians and patients in their decision-making[15]. Among patients on clozapine, longitudinal studies found a significant incidence of weight gain and metabolic syndrome after starting clozapine[13, 16, 17]. Clozapine users have been reported to have a 9% 10-year cardiovascular mortality risk[18], with up to 15.6% experiencing a major cardiovascular event within 21 years of treatment[19]. Network meta-analysis of 100 short-term RCTs with a treatment duration of two to 13 weeks found that among the 18 antipsychotics, clozapine and olanzapine were associated with the largest degree of metabolic dysregulation; and clozapine caused the greatest weight gain and increase in total cholesterol, triglycerides, and glucose[17]. However, a network meta-analysis of 137 mid- and long-term RCTs showed clozapine caused substantial weight gain and cholesterol increases, but not the greatest fasting glucose elevation[20]. Other contrasting results were also seen in some cross-sectional studies, which found that while Clozapine users had higher proportions of diagnosed hypertension, diabetes and dyslipidemia, they had better anthropometric and fasting glucose and lipid levels compared to non-clozapine users and a lower overall cardiovascular disease risk denoted by the Framingham risk score and vascular age[13].

Though RCT is a gold standard for empirical study, its results may have limited generalizability because of the inclusion criteria and dropout rate; in particular, they failed to inform changes to those who had existing cardiovascular and metabolic conditions before treatment. Furthermore, most RCTs had short-term follow-up duration, as the median study duration of included studies in the meta-analysis of the longer-term effects of antipsychotics was only 45 weeks[20]. In addition, although metabolic and cardiovascular disease risk has been examined, limited data compare the actual incidence of major adverse cardiovascular events (MACE) between patients on clozapine and non-clozapine antipsychotics, which represent the severe end of the cardiovascular morbidities. Therefore, the current study aimed to examine the 20-year metabolic risk of patients prescribed clozapine in comparison with non-clozapine SGA antipsychotics in real-world population-based data. The incidence of diabetes mellitus, hypertension, obesity, dyslipidemia, and MACE (defined as a composite of non-fatal myocardial infarction, ischemic stroke, heart failure, and myocarditis), and the development of a single metabolic condition to cardiometabolic multimorbidity (> 2 metabolic conditions) or MACE, were explored. Given that olanzapine

and clozapine are structurally similar[7, 21, 22] with overlapping receptor profiles[21, 23–25], and have both been suggested as antipsychotics most associated with metabolic side effects[17], a direct comparison between clozapine and olanzapine was conducted. Results of this study can provide comprehensive real-world evidence to inform clinical practices and intervention strategies.

Methods

Data source

All data were extracted from the Clinical Data Analysis and Reporting System (CDARS), a centralized clinical data repository containing electronic health records from all public hospitals under the Hong Kong Hospital Authority (HA) management since January 1, 1999. The HA is the principal provider of inpatient and outpatient psychiatric services in Hong Kong, accounting for roughly 90% of psychiatric care for individuals with severe mental illness[26]. The reliability of medication and death recording in CDARS among people with schizophrenia has been validated[27]. This research was approved by the Institutional Review Board (IRB) of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW 23–194). All data were collected anonymously, and the requirement for written patient consent was waived. Reporting adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (eAppendix 1).

Study design and participants

This retrospective cohort study included individuals aged 18 years or older with a diagnosis of schizophrenia (ICD-9-CM code 295) recorded between January 1, 1999, and March 31, 2023. We identified incident clozapine users (ClozUs) as patients who initiated clozapine for the first time between January 1, 2003, and December 31, 2019. For a comparison group, we identified incident users of other antipsychotics (Non-ClozUs) who had no use of clozapine during the observation period and initiated a non-clozapine antipsychotic during the same period. The index date was defined as the date of the first qualifying antipsychotic prescription for each respective group. Patients were required to have at least 90 days of continuous use of the index antipsychotic to ensure adequate exposure.

For each ClozU, three Non-ClozUs (1:3 ratio) were matched using a greedy matching algorithm based on age, sex, and duration of schizophrenia. A progressively relaxed matching criteria on age (± 1 to ± 5 years) and illness duration (± 1 to ± 10 years) was applied to ensure a sufficient number of comparators. The follow-up period for each participant extended from the index date until the first occurrence of an outcome event, death, or the study end date of March 31, 2023.

Outcomes

The primary outcomes were the incidence of major adverse cardiovascular events (MACE), defined as a composite of non-fatal myocardial infarction, ischemic stroke, heart failure, and myocarditis, and the incidence of new-onset metabolic diseases, including diabetes mellitus, hypertension, dyslipidemia, and obesity. All outcomes were identified using their respective ICD-9-CM codes from the CDARS (eTable 1 in the Supplement).

Statistical Analysis

Baseline characteristics were compared between ClozUs and Non-ClozUs using standardized mean differences for continuous variables and chi-square tests for categorical variables. Incidence rates were calculated for each outcome. Cox proportional hazards models estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between clozapine use and each outcome. Individuals with a history of the specific outcome or MACE at or before the index date were excluded from that outcome's analysis. For metabolic outcomes, MACE was treated as a competing risk. Crude HRs were calculated, followed by adjusted HRs (aHRs) controlling for covariates that showed a significant difference at baseline, including educational level, number of prior antipsychotics, number of prior psychiatric hospitalizations, and history of depression, substance use disorders, and alcohol use disorder.

Secondary analyses examined disease progression from a single metabolic condition to cardiometabolic multimorbidity (≥ 2 conditions) or MACE, with between-group differences assessed via chi-square tests. Within the clozapine group, we calculated the incidence rates of metabolic outcomes during the 5 years preceding and following the index date and used Cox models to identify risk factors for incident metabolic disease over the full observation period. A sensitivity analysis repeated the primary analyses comparing

the ClozUs to a 1:1 matched cohort of incident olanzapine users (OlanUs). Given the common clinical use of beta-blockers for clozapine-induced palpitations [28], we reported the proportion of propranolol (a common beta-blocker) use and conducted a sensitivity analysis controlling for prior propranolol use within one year post-index date. All statistical analyses were performed using R, version 4.4.2, with the packages *dplyr*, *tableone*, *cobalt*, *survival*, and *survminer*.

Results

Sample Characteristics

From an initial cohort of 62,279 eligible patients with schizophrenia, we identified 4,783 incident ClozUs and 14,349 matched Non-ClozUs (Fig. 1). Chlorpromazine (13.44%) and olanzapine (9.96%) were among the most incident first- and second-generation antipsychotics separately (eTable 2 in the Supplement). The total cohort had 19132 patients with a mean (SD) age at the index date of 39.42 (11.85) years, with 49.72% female, and the mean (SD) duration of schizophrenia at the index date was 5.57 (4.18) years. After matching, the two groups were well-balanced on age, sex, and duration of schizophrenia (Table 1). However, patients in the ClozU group had a higher level of education (Secondary: 68.8% vs 63.77; tertiary or above: 17.31% vs 16.59%) and had a significantly greater number of previously prescribed antipsychotics (mean [SD], 6.06 [2.93] vs 3.81 [2.04]) and a higher number of psychiatric hospitalizations before the index date (mean [SD], 3.38 [3.91] vs 2.00 [2.89]) (Table 1).

Table 1
Characteristics of the total sample at the index date

	Total	Clozapine	Non-clozapine	*p* value
	N = 19,132	**N = 4,783**	**N = 14,349**	
Age, mean (SD)	39.42 (11.85)	39.41 (11.86)	39.42 (11.85)	0.982
Sex, n (%)				1.000
Female	9512 (49.72)	7134 (49.72)	2378 (49.72)	
Male	9620 (50.28)	2405 (50.28)	7215 (50.28)	
Education level, n(%)				< 0.001
Less than primary	289 (1.51)	55 (1.15)	234 (1.63)	
Primary	2450 (12.81)	566 (11.83)	1884 (13.13)	
Secondary	12411 (64.87)	3261 (68.18)	9150 (63.77)	
Tertiary or above	3209 (16.77)	828 (17.31)	2381 (16.59)	
Unknown	733 (4.04)	73 (1.53)	700 (4.88)	
Duration of schizophrenia at the index date in years, mean (SD)	5.57 (4.18)	5.58 (4.18)	5.56 (4.17)	0.790
Number of antipsychotics prescribed before the index date, mean (SD)	4.37 (2.49)	6.06 (2.93)	3.81 (2.04)	< 0.001
Number of psychiatric hospitalization before the index date, mean (SD)	2.34 (3.23)	3.38 (3.91)	2.00 (2.89)	< 0.001
Clinical conditions before or at the index date, n (%)				
Cancer	748 (3.91)	165 (3.45)	583 (4.06)	0.064
COPD	71 (0.37)	18 (0.38)	53 (0.37)	1.000
Bipolar disorder	1528 (7.99)	398 (8.32)	1130 (7.88)	0.340
Personality disorder	888 (4.64)	245 (5.12)	643 (4.48)	0.074
Anxiety disorder	1117 (5.84)	268 (5.60)	849 (5.92)	0.444
Depression	1997 (10.44)	433 (9.05)	1564 (10.90)	< 0.001
Substance use disorder	1667 (8.71)	325 (6.79)	1342 (9.35)	< 0.001
Alcohol use disorder	522 (2.73)	93 (1.94)	429 (2.99)	< 0.001
Metabolic diseases before or at the index date, n (%)				
MACE	228 (1.19)	52 (1.09)	176 (1.23)	0.489
Diabetes	461 (2.41)	132 (2.76)	329 (2.29)	0.077
Hypertension	390 (2.04)	97 (2.03)	293 (2.04)	1.000
Dyslipidemia	138 (0.72)	31 (0.65)	107 (0.75)	0.554
Obesity	91 (0.48)	27 (0.56)	64 (0.45)	0.363

Incidence and Risk of Metabolic Diseases

Over a mean (SD) follow-up of 12.78 (5.32) years, there was no significant difference in the risk of MACE between the clozapine and non-clozapine groups (aHR, 0.89; 95% CI, 0.76–1.04). After adjusting for baseline covariates, no significantly increased risk in ClozUs of incident diabetes (aHR, 1.00; 95% CI, 0.91–1.11) or dyslipidemia (aHR, 0.91; 95% CI, 0.82–1.02). However, clozapine use was associated with a significantly lower risk of developing hypertension (aHR, 0.75; 95% CI, 0.68–0.83) and obesity (aHR, 0.56; 95% CI, 0.46–0.69) compared to the use of other antipsychotics (Table 2).

Table 2
Incidence and risk of metabolic diseases in clozapine users and non-clozapine users

Cohort name	Cohort size	Mean follow-up duration, years	Number of incident events, n (%)	Crude analysis		Adjusted analysis	
				HR (95% CI)	*p* value	HR (95% CI)	*p* value
MACE Naïve	18,904	12.78 (5.32)	1,064 (5.63)				
Non-clozapine	14,173	12.66 (5.34)	809 (5.71)	1 (ref)	/	1 (ref)	/
Clozapine	4,731	13.13 (5.26)	255 (5.39)	0.90 (0.78–1.04)	0.154	0.92 (0.79–1.08)	0.303
Diabetes Naïve	18,480	12.15 (5.53)	2,430 (13.15)				
Non-clozapine	13,872	12.07 (5.52)	1,755 (12.65)	1 (ref)	/	1 (ref)	/
Clozapine	4,608	12.38 (5.57)	675 (14.65)	**1.12 (1.02–1.22)**	**0.013**	1.00 (0.91–1.11)	0.961
Hypertension Naïve	18,569	12.22 (5.45)	2,652 (14.28)				
Non-clozapine	13,924	12.08 (5.45)	2,023 (14.53)	1 (ref)	/	1 (ref)	/
Clozapine	4,645	12.61 (5.45)	6,29 (13.54)	**0.87 (0.90–0.96)**	**0.003**	**0.76 (0.68–0.84)**	**< 0.001**
Dyslipidemia Naïve	18,784	12.46 (5.36)	2,128 (11.33)				
Non-clozapine	14,083	12.37 (5.37)	1,519 (10.79)	1 (ref)	/	1 (ref)	/
Clozapine	4,701	12.72 (5.34)	609 (12.95)	**1.15 (1.05–1.26)**	**0.004**	0.91 (0.82–1.02)	0.102
Obesity Naïve	18,816	12.66 (5.34)	688 (3.66)				
Non-clozapine	14,111	12.54 (5.36)	542 (3.84)	1 (ref)	/	1 (ref)	/
Clozapine	4,705	13.03 (5.28)	146 (3.10)	**0.76 (0.63–0.91)**	**0.003**	**0.56 (0.46–0.69)**	**< 0.001**

Note. The MACE naïve cohort excluded individuals diagnosed with MACE before the index date. Other naïve cohorts excluded individuals diagnosed with the specific metabolic diseases and MACE before the index date. Adjusted analysis controlled for educational level, number of prior antipsychotics, number of prior

Disease Progression and Risk Factors

The overall rate of progression from a single metabolic disease to cardiometabolic multimorbidity or MACE was significantly lower in the clozapine group compared to the non-clozapine group (32.18% vs 41.31%), but no significant differences between groups for individual conditions (eTable 3 in the Supplement). Sankey diagrams illustrating these deterioration pathways are shown in Fig. 2. Within the clozapine group, the incidence of MACE, diabetes, hypertension, and dyslipidemia was significantly higher in the 5 years following clozapine initiation compared to the 5 years prior, with odds ratios ranging from 1.58 for diabetes to 3.59 for dyslipidemia (eTable 4 in the Supplement). Older age was a consistent risk factor for MACE, diabetes, hypertension, and dyslipidemia, and male sex was a risk factor for MACE (HR, 1.86; 95% CI, 1.18–2.93) in this clozapine group, while a history of anxiety disorder was associated with an increased risk of diabetes, dyslipidemia, and obesity (Table 3).

Table 3
Risk factors associated with incident metabolic diseases after the commencement of clozapine

	MACE		**Diabetes**		**Hypertension**		**Dyslipidemia**		**Obesity**	
	HR (95% CI)	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Age	**1.09 (1.08–1.11)**	**< 0.001**	**1.04 (1.04–1.05)**	**< 0.001**	**1.07 (1.06–1.08)**	**< 0.001**	**1.03 (1.03–1.04)**	**< 0.001**	1.01 (0.99–1.02)	0.36
Sex (ref. female)	**1.50 (1.16–1.94)**	**0.002**	0.87 (0.74–1.02)	0.078	1.40 (1.19–1.64)	< 0.001	0.97 (0.83–1.15)	0.742	0.75 (0.54–1.05)	0.099
Educational level (ref. Less than primary)										
Primary	0.72 (0.35–1.47)	0.372	0.93 (0.50–1.73)	0.821	1.1 (0.51–2.38)	0.801	0.48 (0.25–0.94)	0.033	/	/
Secondary	0.68 (0.34–1.39)	0.295	0.81 (0.44–1.49)	0.502	1.46 (0.68–3.10)	0.331	0.67 (0.35–1.26)	0.213	/	/
Tertiary or above	0.59 (0.27–1.27)	0.178	0.64 (0.34–1.22)	0.174	1.29 (0.60–2.81)	0.515	0.73 (0.38–1.41)	0.353	/	/
Unknown	0.71 (0.25–2.02)	0.519	0.5 (0.19–1.30)	0.158	0.8 (0.28–2.30)	0.684	0.8 (0.33–1.92)	0.611	/	/
Number of antipsychotics prescribed before the index date, mean (SD)	**1.05 (1.01–1.10)**	**0.022**	1.01 (0.98–1.03)	0.701	1.01 (0.99–1.04)	0.306	1.02 (0.99–1.05)	0.221	0.99 (0.93–1.05)	0.725
Number of psychiatric hospitalization before the index date, mean (SD)	0.99 (0.95–1.03)	0.616	1.02 (1.00–1.04)	0.115	**1.03 (1.02–1.05)**	**< 0.001**	**1.03 (1.01–1.05)**	**0.001**	1.03 (0.99–1.07)	0.113
Cancer	0.76 (0.38–1.56)	0.460	1.09 (0.73–1.62)	0.666	1.19 (0.79–1.78)	0.397	1.24 (0.81–1.90)	0.328	1.42 (0.62–3.24)	0.407
COPD	1.77 (0.64–4.93)	0.273	1.08 (0.34–3.38)	0.901	0.9 (0.29–2.84)	0.862	0.47 (0.07–3.37)	0.454	3.09 (0.42–22.59)	0.266
Depression	1.03 (0.64–1.66)	0.894	**1.37 (1.05–1.78)**	**0.019**	0.92 (0.67–1.27)	0.624	1.22 (0.92–1.63)	0.164	1.05 (0.57–1.91)	0.885
Bipolar disorder	1.02 (0.62–1.66)	0.948	1.10 (0.84–1.45)	0.476	1.19 (0.90–1.56)	0.229	0.92 (0.68–1.25)	0.586	0.77 (0.41–1.47)	0.436
Anxiety disorder	1.18 (0.68–2.05)	0.564	1.27 (0.92–1.77)	0.147	1.17 (0.82–1.68)	0.385	1.28 (0.90–1.82)	0.165	0.96 (0.44–2.08)	0.909
Personality disorder	0.88 (0.44–1.76)	0.713	0.97 (0.66–1.44)	0.896	1.28 (0.88–1.86)	0.198	1.08 (0.73–1.60)	0.714	1.67 (0.86–3.26)	0.132

	MACE		Diabetes		Hypertension		Dyslipidemia		Obesity	
	HR (95% CI)	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Substance use disorder	1.58 (0.87–2.88)	0.131	1.17 (0.83–1.64)	0.383	1.14 (0.79–1.65)	0.488	**1.55 (1.12–2.15)**	**0.009**	**1.95 (1.09–3.49)**	**0.025**
Alcohol use disorder	1.15 (0.53–2.46)	0.725	0.93 (0.52–1.66)	0.798	1.12 (0.67–1.89)	0.657	**0.42 (0.18–0.96)**	**0.039**	0.25 (0.03–1.86)	0.175

Sensitivity Analysis

We matched 4,783 incident OlanUs to ClozUs (eTable 5 in the Supplement). ClozUs were associated with a lower risk of hypertension (aHR, 0.84; 95% CI, 0.75–0.95), dyslipidemia (aHR, 0.85; 95% CI, 0.76–0.96), and obesity (aHR, 0.67; 95% CI, 0.53–0.85) (eTable 6 in the Supplement) in comparison with OlanUs after adjusting for covariates. Propranolol use within one year was significantly higher in ClozUs (35.5%) compared to both Non-ClozUs (18.1%) and OlanUs (21.5%) (eTable 7 in the Supplement). However, the results after controlling for prior propranolol use were generally consistent with the main results (eTable 8–9 in the Supplement).

Discussion

The present population-based cohort study investigated the long-term cardiometabolic risks associated with clozapine use in a real-world clinical setting in Hong Kong. Our findings indicate that ClozUs had comparable risks of MACE, diabetes, and dyslipidemia, but lower risks of hypertension and obesity versus Non-ClozUs, despite an overall increase in metabolic comorbidities after clozapine use. Furthermore, clozapine was associated with a lower rate of metabolic disease progression from a single condition to multimorbidity or MACE versus Non-ClozUs. Direct comparison with olanzapine revealed ClozUs had lower incident risk for hypertension, dyslipidemia and obesity. Within ClozUs, advanced age, number of prior antipsychotic use and psychiatric hospitalization, and history of depression and substance use were associated with higher risks of metabolic diseases.

Despite the overall increase in metabolic comorbidities after clozapine use, we found lower adjusted and unadjusted incidence of hypertension and obesity in ClozUs compared with Non-ClozUs, diverging from previous meta-analyses of RCTs[17, 20]. Results held after controlling for the commonly prescribed beta-blocker (propranolol). This discrepancy may reflect several factors inherent to real-world clinical practice. First, ClozUs in Hong Kong often receive relatively low dosages; a local study found approximately half were prescribed ≤ 300 mg/day[29]. Given that metabolic side effects are often dose-dependent[30], this may mitigate the risk of weight gain and hypertensive effects. Second, mandatory white blood cell monitoring for ClozUs and consequent clinical reviews may facilitate earlier detection and more proactive management of metabolic disturbances than occurs with other antipsychotics, despite a shared annual metabolic profile monitoring frequency based on the Hong Kong treatment guideline, a phenomenon sometimes termed the "monitoring effect"[13, 31]. A recent Australian study of TRS patients similarly found no significant differences in diabetes, obesity, or hypertension between ClozUs and Non-ClozUs, suggesting a comprehensive approach targeting broad risk factors, not clozapine alone, when evaluating metabolic problems in TRS[31]. Third, the comparator group included all non-clozapine antipsychotics, including metabolically liable agents like quetiapine and olanzapine, potentially elevating the comparator group's metabolic burden.

One notable finding is that clozapine's significantly elevated unadjusted risks of diabetes and dyslipidemia became insignificant after controlling for illness duration, number of hospitalizations, and comorbid psychiatric conditions. Similarly, in the sensitivity analysis comparing clozapine with olanzapine, clozapine showed a higher unadjusted risk of incident diabetes but lower adjusted risks of hypertension, dyslipidemia, and obesity, contrasting with a recent meta-analysis of observational studies that found olanzapine had a lower risk of new-onset diabetes[32]. Notably, number of prior antipsychotic use and psychiatric hospitalization, and history of depression and substance use were associated with higher metabolic risks in ClozUs. These results highlighted a complex relationship between antipsychotics and the development of metabolic conditions. On one hand, clozapine may exert a more pronounced, direct effect on glucose metabolism and insulin resistance[6, 32, 33], given its unique receptor pharmacology, including antagonism of muscarinic M3 receptors on pancreatic β-cells and disruption of insulin signaling cascades via inflammatory cytokines such as IL-6 and TNF-α. This may specifically predispose patients to glucose dysregulation independent of weight gain[33]. On the other hand, cumulative illness

burden and psychiatric comorbidities commonly associated with TRS may also play a prominent role in elevating metabolic risk after clozapine initiation.

The finding that MACE incidence did not differ significantly between ClozUs and Non-ClozUs aligns with prior autopsy studies[34] and cardiovascular mortality in retrospective cohorts[35]. Clozapine's superior efficacy in improving symptoms, self-care, and overall survival may offset some of its direct cardiovascular risks[11, 36]. A large nationwide Finnish cohort study demonstrated that clozapine was associated with the lowest all-cause mortality among all antipsychotics[9], suggesting that the net clinical benefit of clozapine, including its effects on suicide prevention, reduced aggression, and better treatment adherence, may attenuate the death related to cardiovascular risk. To our knowledge, this study is among the first to demonstrate that fewer ClozUs develop metabolic or cardiometabolic multimorbidity or MACE from a single condition. It is possible that the mandatory hematological monitoring inherent to clozapine prescribing creates a framework for frequent clinical contact, which may facilitate the timely identification and management of emerging cardiovascular risk factors before they progress to MACE and delay the development of cardiometabolic multimorbidity. Recent literature emphasizes that comprehensive cardiometabolic monitoring and aggressive treatment of physical health comorbidities are essential to reducing the mortality gap in schizophrenia[31]. Therefore, a structured, protocol-driven cardiometabolic monitoring and management programme should be specifically implemented for people on antipsychotics, including clozapine, to mitigate the metabolic burden of these medications.

Consistent with general population trends and previous psychiatric literature[17], older age and male sex were identified risk factors for metabolic disorders among clozapine patients. The higher MACE risk in male patients likely reflects sex-specific cardiovascular risk trajectories, including higher rates of smoking, abdominal adiposity, and less favourable lipid profiles in men with schizophrenia[7]. Furthermore, comorbid depression and substance use disorder were significantly associated with an increased risk of diabetes, dyslipidemia, and obesity among ClozUs. Mood disorders are increasingly recognized as sharing pathophysiological pathways with metabolic syndrome, involving chronic systemic inflammation, hypothalamic-pituitary-adrenal (HPA) axis hyperactivity, and elevated pro-inflammatory cytokines (e.g., IL-6, TNF-α)[37]. Chronic cortisol elevation secondary to HPA axis dysregulation promotes visceral adiposity, insulin resistance, and dyslipidemia, potentially acting synergistically with clozapine's receptor profile to amplify metabolic risk[37]. Previous evidence also suggests that schizophrenia patients comorbid with substance use disorder face a higher risk of physical comorbidities, including cardiovascular, metabolic, and infectious diseases[38]. These findings necessitate heightened cardiometabolic vigilance in patients with comorbid depression or substance use disorder and support integrating psychiatric and physical health monitoring in this vulnerable population. Algorithm-based personalized risk models[39, 40]may also aid early management and prevention of metabolic comorbidities.

Study Strengths and Limitations

This study has several strengths. It used a comprehensive population-based electronic health record system, capturing longitudinal clinical and pharmacological data to reduce selection bias. It assessed the full cardiometabolic spectrum, from incident conditions to MACE and cardiometabolic multimorbidity, providing a thorough evaluation. With a mean follow-up of 12.8 years (up to 20 years), it offers one of the longest observational periods for assessing antipsychotic metabolic effects. The primary analysis compared clozapine with non-clozapine antipsychotics, while a sensitivity analysis directly contrasted clozapine and olanzapine, isolating relative risks between these high-risk agents. Several limitations warrant consideration. First, ICD-9-CM coding may underestimate metabolic condition incidence, as undiagnosed or unrecorded cases are missed, especially with infrequent healthcare contact. Second, Despite matching for illness duration and adjusting for prior hospitalizations, unmeasured confounders like lifestyle factors, smoking, and antipsychotic polypharmacy could influence results. Third, selection bias may exist: the 90-day stability requirement likely excluded early clozapine discontinuers due to acute adverse effects, potentially selecting a metabolically resilient population. The ClozUs group also had lower baseline depression and substance use disorder rates, suggesting possible indication bias despite adjustment. Fourth, the low observed obesity rate likely reflects underascertainment from ICD-9 codes rather than BMI measurement. Fifth, conducted in a predominantly Chinese Hong Kong population, findings may not fully generalize to other ethnic groups or healthcare systems with different monitoring standards. Finally, while propranolol use was controlled as a proxy for clozapine-related tachycardia, other metabolic-influencing medications (e.g., antidepressants, mood stabilizers, lipid-lowering agents) were not fully accounted for.

Conclusions

In a real-world clinical setting, ClozUs was found to have a comparable incidence risk of diabetes, dyslipidemia, and MACE, a lower incidence risk of hypertension and obesity, and a lower risk of metabolic disease progression compared with Non-ClozUs. Therefore, metabolic concerns should not be a barrier to clozapine prescription in patients with TRS. However, personalized, structured, and protocol-based cardiometabolic monitoring and management programs would be important for both ClozUs and Non-ClozUs to reduce the development of cardiometabolic comorbidities.

Declarations

Author Contribution:

Drs Zhou and Chan had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr Chan is the corresponding author.

Concept and design: Zhou, Luo, Siskind, Chan.

Acquisition, analysis, or interpretation of data: Zhou, Hui, Luo, Halstead, Siskind, Perry, Osimo, Murray, Chan.

Drafting of the manuscript: Zhou, Hui, Chan.

Critical revision of the manuscript for important intellectual content: Zhou, Hui, Luo, Tang, Lui, Lee, Halstead, Siskind, Perry, Osimo, Murray, Chan.

Obtained funding: Chan.

Administrative, technical, or material support: Tang, Chan.

Supervision: Luo, Siskind, Chan.

Conflict of Interest Disclosure: Dr Murray reported consulting for Ieso Digital Health and Bristol Myers Squibb. Dr Perry is appointed Topic Advisor to the National Institute of Health and Care Excellence (NICE) for Severe and Enduring Mental Illness. Dr Perry is a member of the Governance Board for the Medicines and Healthcare products Regulatory Agency (MHRA) Digital Mental Health Technologies AI Sandbox. No other disclosures were reported.

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Data Sharing Statement: The data is part of the registry data and cannot be made available publicly.

AI Disclosure Statement: The authors used *Claude Opus 4.6* solely to refine, edit, and format text originally written by the authors, including grammar, spelling, clarity, and style improvements. The AI tools were not used to generate the manuscript's substantive scientific content, data, analyses, results, or conclusions. All authors reviewed and verified the revised text and take full responsibility for the accuracy, integrity, and final content of the manuscript.

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Figures

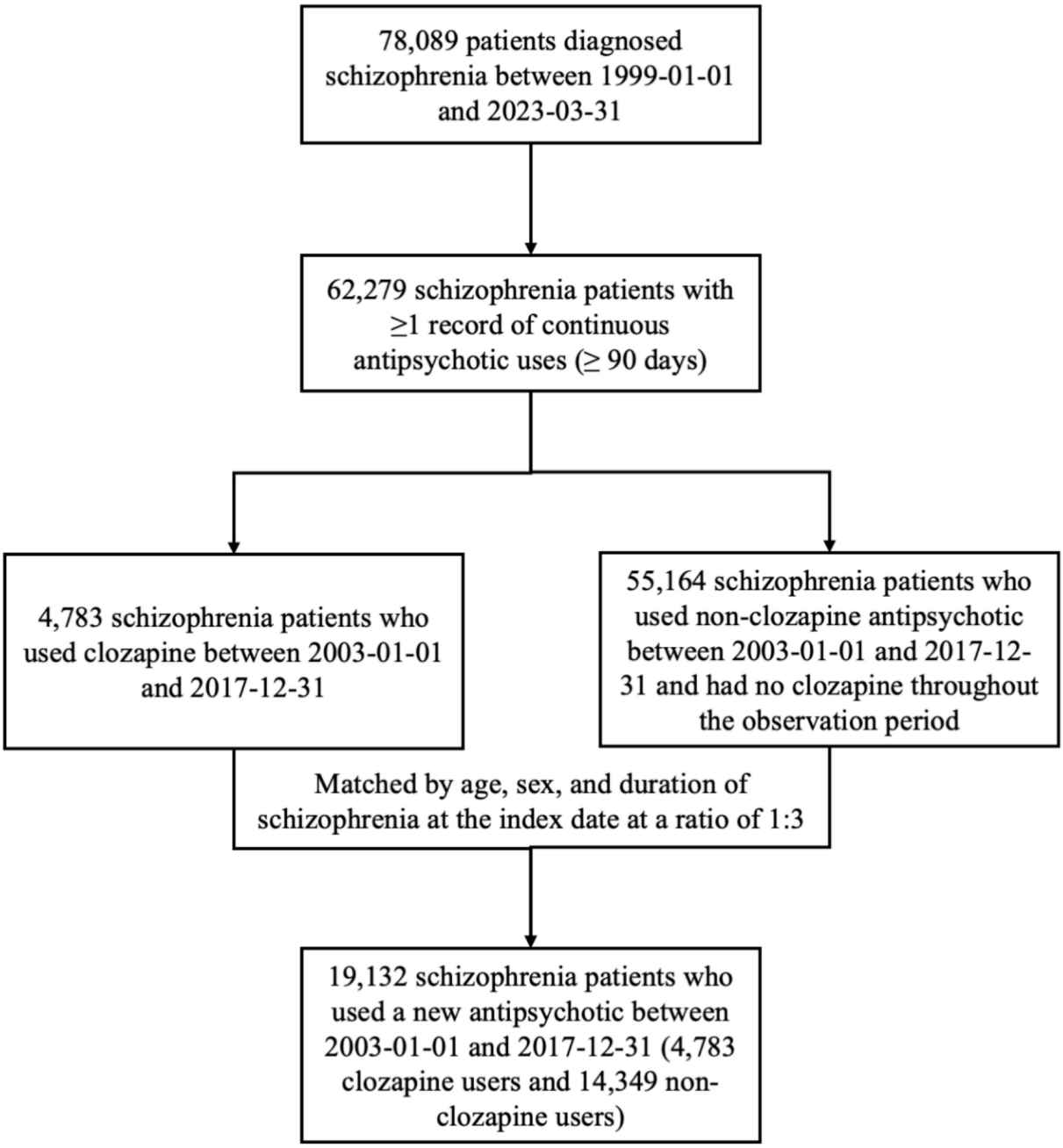
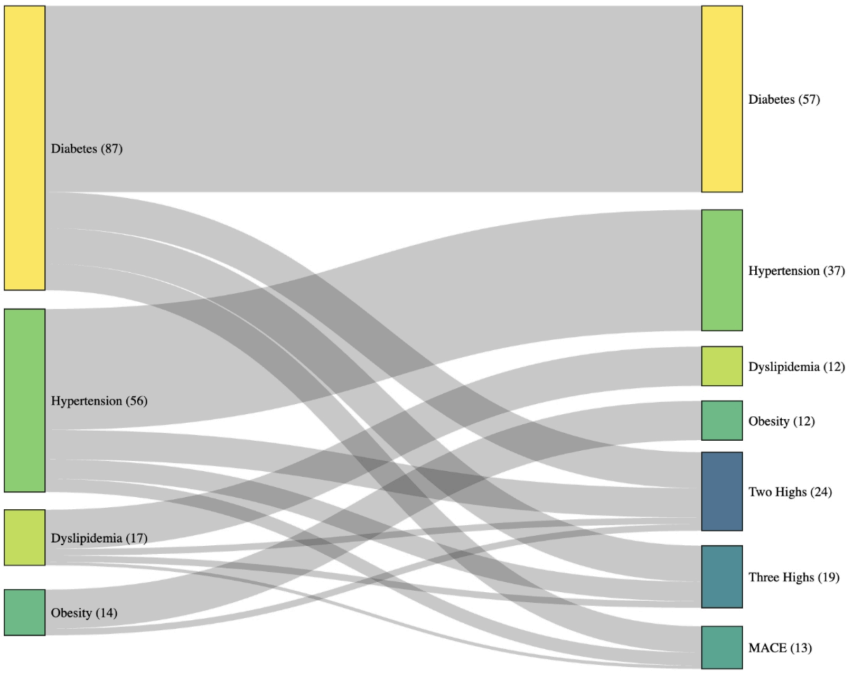
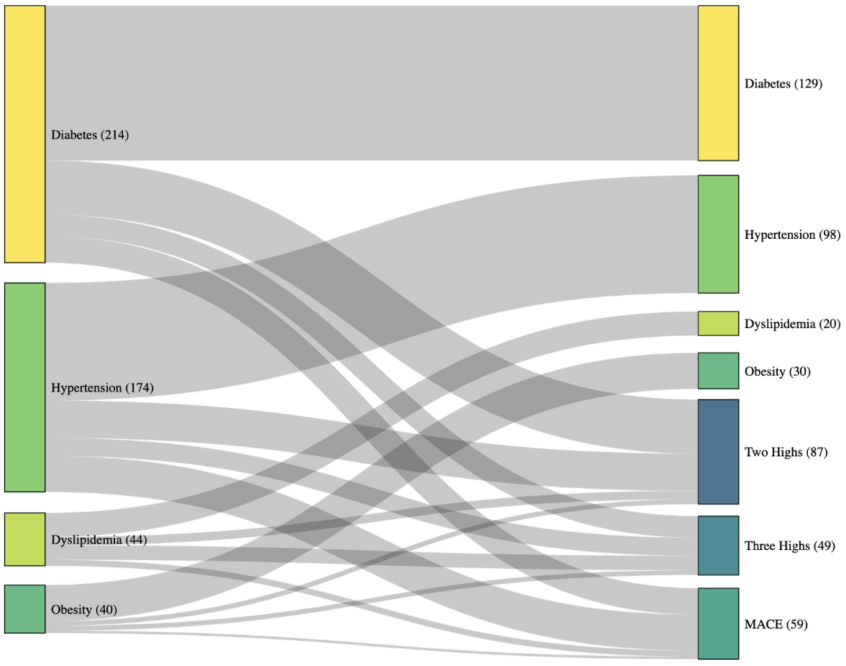


Figure 1

Flowchart of sample inclusion



(a)



(b)

Figure 2

Deterioration pathways from single metabolic disease to severe multimorbidity (i.e., MACE, Two Highs, Three Highs)

Supplementary Files

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- SupplementaryMetabolicRiskMolecularPsychiatry.docx